Comparative Effectiveness Review
Number 190

Treatment of Osteoarthritis of the Knee: An Update Review

Comparative Effectiveness Review

Number 190

Treatment of Osteoarthritis of the Knee: An Update Review

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. 290-2015-00010-I

Prepared by:
RAND Southern California Evidence-based Practice Center
Santa Monica, CA

Investigators:
Sydne J. Newberry, Ph.D.
John FitzGerald, M.D., Ph.D.
Nelson F. SooHoo, M.D.
Marika Booth, M.S.
Joyce Marks, B.S.
Aneesa Motala, B.A.
Eric Apaydin, M.S., M.P.P.
Christine Chen, M.D.
Laura Raaen, M.P.H.
Roberta Shanman, M.L.S.
Paul G. Shekelle, M.D, Ph.D.

AHRQ Publication No. 17-EHC011-EF
May 2017

This report is based on research conducted by the Southern California Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00010-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EffectiveHealthCare@ahrq.hhs.gov.

Suggested citation: Newberry SJ, FitzGerald J, SooHoo NF, Booth M, Marks J, Motala A, Apaydin E, Chen C, Raaen L, Shanman R, Shekelle PG. Treatment of Osteoarthritis of the Knee: An Update Review. Comparative Effectiveness Review No. 190. (Prepared by the RAND Southern California Evidence-based Practice Center under Contract No. 290-2015-00010-I.) AHRQ Publication No.17-EHC011-EF. Rockville, MD: Agency for Healthcare Research and Quality; May 2017. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
DOI: https://doi.org/10.23970/AHRQEPCCER190.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officers named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

Sharon B. Arnold, Ph.D.
Acting Director
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.
Director, Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Kim Wittenberg, M.A.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Laura Pincock, Pharm.D., M.P.H.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Acknowledgments

The authors gratefully acknowledge Patricia Smith for her administrative support on the project.

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who provided input to this report follows:

David Felson, M.D.
Boston University
Boston, MA

Mark D. Grant, M.D., Ph.D.*
Blue Cross Blue Shield Association
Chicago, IL

David S. Jevsevar, M.D., M.B.A.*
Geisel School of Medicine at Dartmouth
Hanover, NH

Jeffrey N. Katz, M.D., M.S.*
Brigham and Women's Hospital
Boston, MA

Julie J. Keysor, Ph.D, P.T.*
Boston University
Boston, MA

Gayle Lester, Ph.D. *
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
Bethesda, MD

Jyme Schafer, M.D., M.P.H.
Centers for Medicare & Medicaid Services
Baltimore, MD

Neil Segal, M.D.*
Dr. George Varghese Professor of Rehabilitation Medicine
Department of Rehabilitation Medicine
University of Kansas Medical Center
Kansas City, KS

*Provided input on Draft Report.

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

The list of Peer Reviewers follows:

Rowland W. Chang, M.D., M.P.H
Northwestern University Feinberg School of Medicine
Chicago, IL

G. Kelley Fitzgerald, P.T., Ph.D., FAPTA
University of Pittsburgh
Pittsburgh, PA

Nancy Lane, M.D.
Department of Internal Medicine
University of California, Davis
Davis, CA

Jamal Mikdashi, M.D.
Associate Professor
University of Maryland School of Medicine
Baltimore, MD

Treatment of Osteoarthritis of the Knee: An Update Review

Structured Abstract

Objectives. To assess the evidence for the efficacy of the following interventions for improving clinical outcomes in adults with osteoarthritis (OA) of the knee: cell-based therapies; glucosamine, chondroitin, or glucosamine plus chondroitin; strength training, agility, or aerobic exercise (land or water based); balneotherapy, mud bath therapy; electrical stimulation techniques (including transcutaneous electrical stimulation [TENS], neuromuscular electrical stimulation, and pulsed electromagnetic field therapy [PEMF]); whole body vibration; heat, infrared, or ultrasound; orthoses (knee braces, shoe inserts, or specially designed shoes); weight loss diets; and home-based therapy or self-management.

Data sources. PubMed®, Embase®, the Cochrane Collection, Web of Science, and the Physiotherapy Evidence Database (PEDRO) from 2006 to September 2016, and ClinicalTrials.gov and the proceedings from the 2015 American College of Rheumatology annual meetings.

Review methods. We included randomized controlled trials conducted in adults 18 years or over diagnosed with OA of the knee, comparing any of the interventions of interest with placebo (sham) or any other intervention of interest that reported a clinical outcome (including pain, function, and quality of life). We also included single-arm and prospective observational studies that analyzed the effects of weight loss in individuals with OA of the knee on a clinical outcome. Standard methods were used for data abstraction and analysis, assessment of study quality, and assessment of the quality of the evidence, according to the Agency for Healthcare Research and Quality Methods Guide. Findings were stratified according to duration of interventions and outcomes: short term (4–12 weeks), medium term (12–26 weeks), and long term (>26 weeks).

Results. Evidence was insufficient to draw conclusions about the effectiveness of many interventions, largely due to heterogeneous and poor-quality study design, which limited the number of studies that met inclusion criteria and could be pooled.

Interventions that show beneficial effects on short-term outcomes of interest include TENS for pain (moderate strength of evidence [SoE]); strength and resistance training on Western Ontario and McMaster University Arthritis Index (WOMAC) total scores; tai chi on pain and function; and agility training, home-based programs, and PEMF on pain (low SoE).

Interventions that show beneficial effects on medium-term outcomes include weight loss for pain (moderate SoE) and function, **intra-articular platelet-rich plasma on pain and quality** of life, **glucosamine plus chondroitin on pain and function**, **chondroitin sulfate alone on pain,** general exercise programs on pain and function, tai chi on pain and function, whole-body vibration on function, and home-based programs on pain and function (low SoE).

Interventions that show beneficial long-term effects include agility training and general exercise programs for pain and function, and manual therapy and weight loss for pain (low SoE). Moderate SoE supports a lack of long-term benefit of glucosamine-chondroitin on pain or

function, and glucosamine or chondroitin sulfate alone on pain. No consistent serious adverse effects were reported for any intervention.

Almost no studies conducted subgroup analysis to assess the participant characteristics associated with better outcomes, and few studies systematically compared interventions head to head. Additional limitations included lack of blinding and sham controls in studies of physical interventions and the potentially limited applicability of study results to patients seen in nonacademic health care settings.

Conclusions. A variety of interventions assessed for their efficacy in treating OA of the knee in this review demonstrate shorter term beneficial effects on pain and function. With the exception of weight loss, agility training, and general exercise programs, few have been tested for or show long-term benefits. Larger randomized controlled trials are needed, with more attention to appropriate comparison groups and longer duration, to assess newer therapies and to determine which types of interventions are most effective for which patients.

Contents

Tables

Figures

Appendixes

Executive Summary

Background and Objectives

Osteoarthritis (OA) of the knee is a highly prevalent condition among adults, characterized by the progressive destruction of the cartilage that lines the knee joints, the subchondral bone surfaces, and synovium, accompanied by pain, immobility, muscle weakness, and reduction in function and the ability to complete activities of daily living (ADLs). Two types of OA of the knee are recognized: the more prevalent primary OA of the knee is the result of the progressive joint cartilage destruction over time, whereas secondary OA of the knee can be caused by trauma, inactivity, overweight, or a disease process such as rheumatoid arthritis. No evidence suggests that the two types are treated differently or respond differently to treatments.[1] Therefore, the remainder of this report treats the two conditions as one entity. The clinical diagnosis of OA of the knee is typically based on presentation, including insidious onset of weight-bearing knee pain that is exacerbated by use of the joint and relieved by rest, and that tends to worsen over the course of the day. Radiographic evidence of OA may precede symptomatic OA but may not correlate with symptom severity. Radiologic severity can be estimated and expressed using the Kellgren and Lawrence (K-L) criteria. However, a number of versions of the criteria exist: At less severe grades, correlation with symptoms is poor,[2] whereas at more severe grades, agreement tends to be higher. The primary impact of these different versions of the criteria may be the challenge that they create in trying to assess, compare, and pool the findings of research studies.[2] Some longitudinal studies have even used different criteria at different time points within the same study. Because of the variation in scores for radiographic finding under various versions of the criteria (especially for individuals with less-advanced disease), stratification is important. Some evidence suggests that among individuals with knee pain, magnetic resonance imaging (MRI) demonstrates physical signs of osteoarthritic changes in the knee before they are visible radiographically.[3] However, the sensitivity and specificity of MRI in diagnosis and monitoring of progression have not yet been definitively demonstrated and are not yet used in clinical practice.

The goals of treatment for OA of the knee include relief of pain and inflammation, and improvement in or maintenance of mobility, function (including activities of daily living [ADLs]), and health-related quality of life (HRQoL). Although numerous treatment strategies have been implemented, from the least intense (analgesics) to the most intense (knee replacement [TKR] surgery), it has remained unclear which treatments or combinations of treatments are most effective for which populations. Whereas the efficacy of TKR for improving pain and function has been demonstrated, not all patients are candidates for this surgery. In addition, TKR may not be a permanent solution, as surgery may need to be repeated within two decades. Thus, effective treatments need to be identified that can relieve pain and improve function to delay or avert surgery.

Treatment options for OA of the knee include analgesics, cell-based therapies and other agents that aim to halt or reverse joint damage, physical interventions aimed at restoring or improving function, and others. Information on the Food and Drug Administration (FDA) approval status, indications, and warnings for the treatments included in this review is included in Appendix G.

Numerous recent evidence-based treatment guidelines have been issued, including the 2012 American College of Rheumatology (ACR) Guidelines[4] and the 2013 American Academy of Orthopaedic Surgeons (AAOS) guidelines for the treatment of OA of the knee. These guidelines are not in total agreement about the recommended treatments: For example the 2012 ACR Guidelines conditionally recommend hyaluronic acid (HA), while the AAOS guidelines recommend against its use to treat patients with symptomatic conditions.[5]

Scope and Key Questions

Scope of the Review

Systematic reviews have been conducted on many of the interventions used to treat OA of the knee, including four reviews by Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers since 2007.[1, 6-8] Uncertainty continues to surround the use of all treatments intended as disease-modifying agents (including intra-articular hyaluronic acid [HA] and glucosamine and chondroitin), acupuncture, physical therapy, exercise, braces and orthotics, and arthroscopic lavage, as well as the comparative efficacy and safety of oral, topical, and intraarticular analgesics and anti-inflammatories.

This review is part of a continuous update review process that aims to repeatedly assess the need to update—and then to update if needed—a systematic review that was conducted in 2007[1] that assessed the efficacy and safety of HA, glucosamine and/or chondroitin, and arthroscopic surgery (the title of the original review, "Treatment of Primary and Secondary OA of the Knee: an Update Review," was changed to "Treatment of OA of the Knee"). Prior to preparing this review, we conducted an updating surveillance assessment that comprised an environmental scan and consultation with a technical expert panel (TEP) to assess the currency of the conclusions of the 2007 review.[9] A document that summarized the findings of this bifurcated process was posted for public review.[10]

The environmental scan did not support a need to update the topics of intra-articular HA and arthroscopic surgery. However, we identified at least one large recent trial on glucosamine-chondroitin that prompted us to want to update the review on this topic.

The TEP for the surveillance process uniformly advised us that the conclusions of the 2007 report for intraarticular HA, oral glucosamine chondroitin, and arthroscopic surgery remained current and did not need updating. Instead, they suggested reviewing cell-based therapies, physical interventions, SNRIs (serotonin–norepinephrine reuptake inhibitor), topical agents, weight loss, and acupuncture. The TEP for the current review concurred with the suggestions of the TEP for the surveillance report and also requested inclusion of home-based and self-management therapies.

The treatment modalities selected for inclusion in this review reflect a combination of the findings of the environmental scan, the TEP for the Surveillance process, the public comments, and the TEP for this review. These modalities include glucosamine and chondroitin, cell-based therapies, physical interventions, weight loss, home-based therapies, and self-management. As a 2012 SR by another EPC reviewed the effects of the physical interventions,[7] we made the decision that as part of this review, we would update the findings of that review. Topics not included in the current report (e.g., intraarticular corticosteroids, SNRIs, topical agents, and acupuncture, as well as HA) may need to be addressed in a future review.

The protocol has been published on the AHRQ Effective Health Care Web site (http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2247).

Key Questions

Based on the findings of the environmental scan, TEP assessments, and public comments, the Key Questions from the 2007 report were revised as follows.

Key Question 1a: What is the clinical effectiveness of cell-based therapies, oral glucosamine and/or chondroitin, physical treatment interventions, weight loss, or home-based and self-management therapies in patients with OA of the knee, compared with appropriate placebo/sham controls or compared with other active interventions?

Key Question 1b: How do the outcomes of each intervention differ by the following population and study characteristics: sex, disease subtype (lateral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

Key Question 2a: What harms are associated with each intervention in patients with OA of the knee?

Key Question 2b: How do the harms associated with each intervention differ by the following population or study characteristics: sex, disease subtype (lateral tibiofemoral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

Analytic Framework

The review was guided by the analytic framework shown in Figure A.

Figure A. Analytic framework for osteoarthritis of the knee

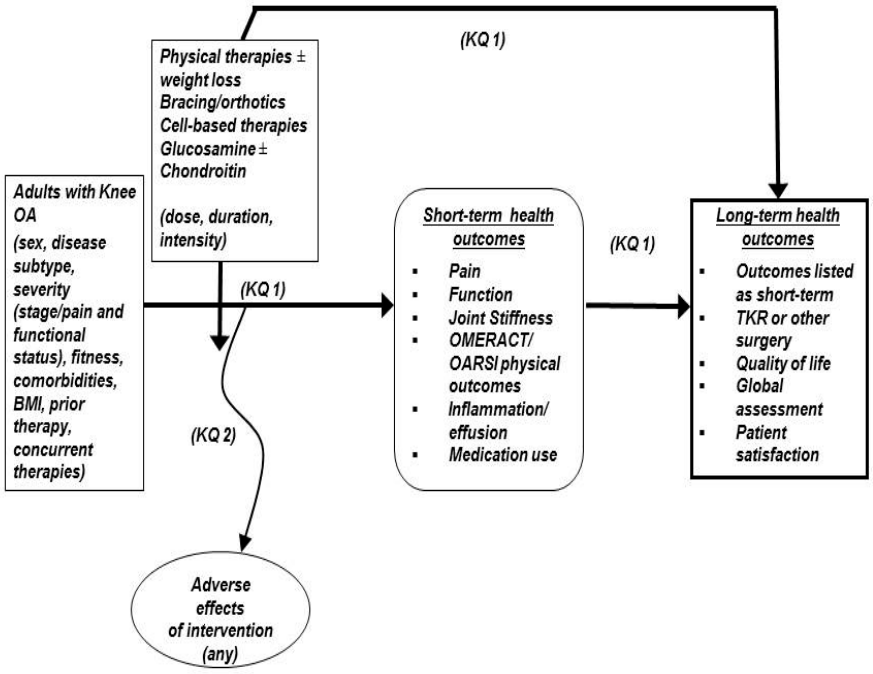


Figure notes: BMI = Body Mass Index; KQ = Key Question; OA = Osteoarthritis; OARSI = Osteoarthritis Research Society International; OMERACT = Outcome Measures in Rheumatology; TKR = Total Knee Replacement.

Methods

The methods used to conduct the systematic review portion of this continuous update are based on the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[9] Systematic searches of electronic databases were designed and conducted to identify English language studies and those with an English–language abstract that enrolled participants with a confirmed diagnosis of osteoarthritis of the knee. Searches were supplemented by references identified by TEP members and content experts, who hand-searched recent relevant conference proceedings. The inclusion/exclusion criteria by target population, interventions, outcomes, comparators, setting, and study duration are shown in Table 1 of the full report. We limited included studies for assessment of efficacy to randomized controlled trials, with the exception of studies that assessed the effects of weight loss, for which we also included single-arm trials and prospective cohort studies. We included prospective observational studies and case reports that reported on adverse events associated with use of the interventions of interest for the treatment of OA of the knee. Conference proceedings and letters that reported sufficient information to enable assessment of risk of bias and that reported unique data were included. Relevant systematic reviews were also considered for inclusion.

The searches commenced with the year 2006, one year prior to the latest search dates of the original review of glucosamine and chondroitin that we are updating.[7] However, because we are also updating topics covered in an EPC review on physical interventions for the treatment of pain in patients with OA of the knee that was conducted in 2012,[11] we did not re-review studies included in (or actively excluded from) that review unless the study included a treatment group of interest that the original review did not evaluate. An update search was conducted in September 2016.

In addition, relevant stakeholders, including manufacturers of over-the-counter and prescription medications and medical devices used to treat OA of the knee were contacted by the Scientific Resource Center for scientific information packets that contain any unpublished information on the efficacy and/or safety of their products when used specifically to treat OA of the knee; no information was obtained from manufacturers. A notice was also placed in the Federal Register requesting any relevant information on the use of dietary supplements containing glucosamine or chondroitin to treat OA of the knee.

Pairs of experienced literature reviewers screened titles identified by literature searches using pre-specified criteria, without reconciliation of decisions. Abstracts of those titles selected for inclusion by one or both reviewers were dually screened using prespecified criteria, with disagreements reconciled by the project leaders, if necessary. Full text articles or other documents were obtained for included abstracts. DistillerSR™ software was used for screening, abstraction, reconciliation, and tracking. Any references that were suggested by members of the TEP, peer reviewers, or public reviewers were obtained and underwent the same screening and abstraction process. Reference lists from recent systematic reviews on the topics of interest were also screened for relevant articles that had not appeared in the search output.

We also conducted an update search during peer review and included any relevant studies from the update search in the final report. Study-level details and data were dually abstracted by reviewers, who also rated the quality of studies for RCTs using a modified Cochrane Risk of Bias (RoB) tool and for adverse events (AE)s using a modified McHarms tool. The study-level details and outcomes are presented in an evidence table in Appendix C; the results of risk-of-bias assessment are presented in a table in Appendix F.

Outcome data were stratified by length of time from baseline. Short-term outcomes were 4 to less than 12 weeks, medium-term outcomes were 12 to 26 weeks, and long-term outcomes were longer than 26 weeks. If a study reported outcomes at more than one short-, medium-, or long-term time period, we abstracted the longer one(s). Effect sizes and confidence intervals were calculated for each outcome based on differences at follow-up (baseline values were assumed to be statistically similar). If three or more studies reported the same outcome measure for the same intervention during the same follow-up time period, we pooled the outcomes using the Hartung Knapp method for random effects meta-analysis.[12] Because some studies did not report the scales used for outcome measures and because it was not always possible to determine the scales from the data, we report pooled outcomes as standardized mean differences; we did not pool studies that used different tools to measure a similar outcome (e.g., visual analog Scale [VAS] and Western Ontario and McMaster University Arthritis Index [WOMAC] pain measures), as two tools used in the same study on the same participant population sometimes resulted in different outcomes. If a study reported outcomes for pain or function using multiple outcome measures, all outcomes were abstracted, but WOMAC outcomes were given preference in analyses. The findings of meta-analyses are reported quantitatively with forest plots in the main text. All studies for which results are included in the report are described qualitatively (narratively) by the

type of intervention and the duration of followup. Descriptions of studies of similar interventions were grouped by outcome measures when feasible.

We also assessed whether significant standardized mean differences of pooled outcomes met a pre-specified minimum clinically important difference (MCID). If studies reported whether their outcomes met a MCID or reported on the percent of participants who achieved a response, we noted that in the narrative descriptions. We rated the strength of evidence (SoE) of each intervention-outcome-followup time based on the AHRQ Methods Guide. Domains include study limitations (study design, risk of bias [RoB], and overall methodological quality), consistency of the direction of effect sizes across studies, precision of the estimate (including number of studies), directness of the relationship between outcomes measured and the outcomes of interest, and magnitude of the effect size.

For outcomes for which no pooling was possible, we estimated a rating based on qualitative assessment of the individual studies that met the inclusion criteria. Overall strength of evidence was assessed identically as for pooled studies (considering study design and average RoB) (Appendix E). Consistency was assessed as the direction of the reported effect across studies (or within studies if a single RCT used multiple tools to measure the same outcome), precision was assessed in terms of the similarity in effect sizes, the average variance, and the numbers of studies. Directness was assessed as it would be for pooled outcomes. Lack of pooling automatically decreased the SoE grade by one unit.

Based on these domains, we rated the SoE for each comparison of interest as high, moderate, low, or insufficient (if no or too few studies were identified that addressed the outcome). We rated applicability of participant populations and interventions separately, as described below.

Peer Review and Public Commentary

A draft version of the draft report was posted for peer review and for public comments on September 12, 2016, and revised in response to comments. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

We identified 107 studies that met inclusion criteria for assessing the efficacy of interventions for treating OA and 57 studies that reported on adverse events (AEs). Our literature flow diagram (Figure B) displays our screening results. Appendix D contains our data abstraction tools that were used for abstracting the data of the 107 included studies. This section presents the key points for each treatment modality and the strength of the evidence for conclusions.

Figure B. Literature flow diagram

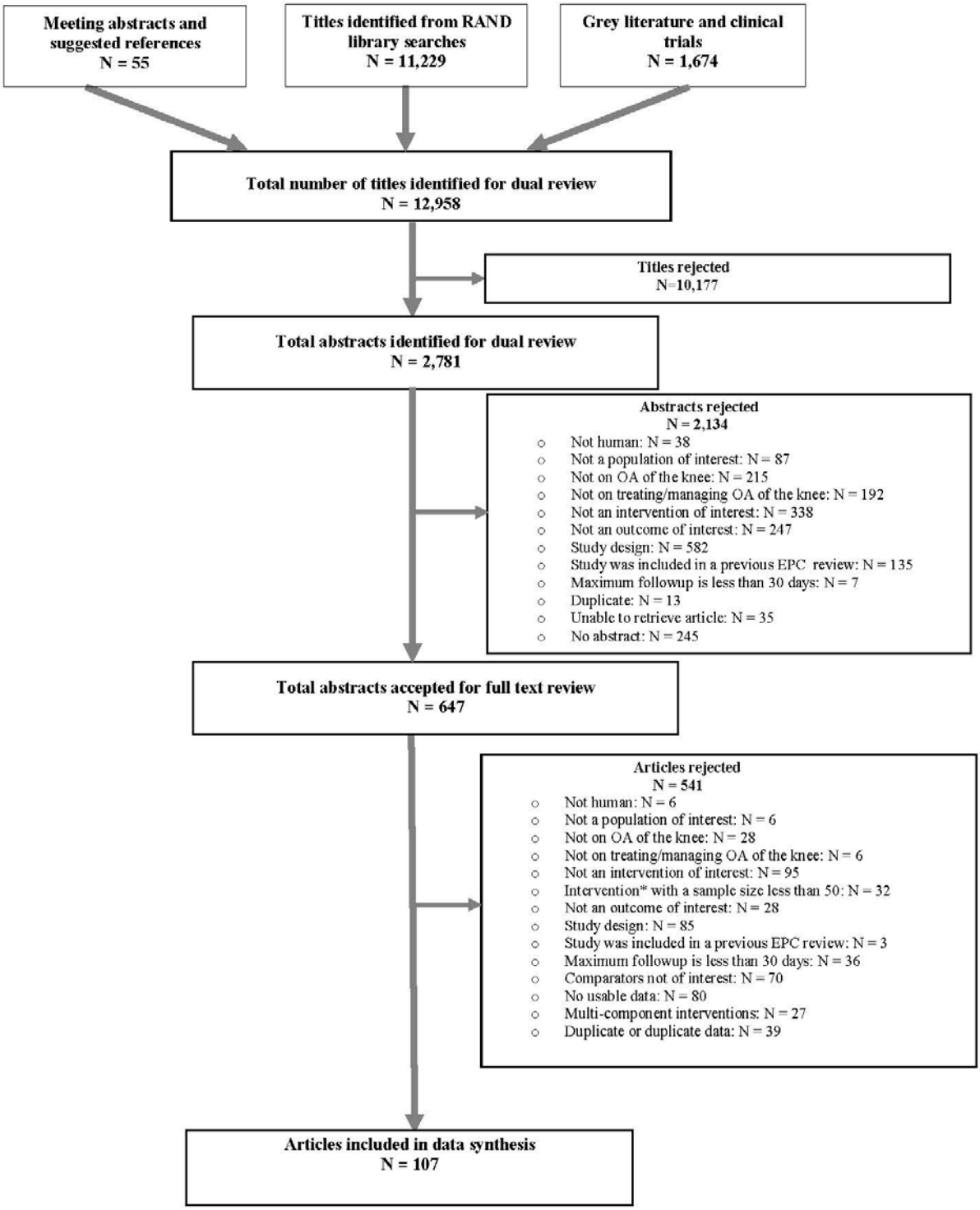


Figure notes: *Studies of glucosamine and/or chondroitin that enrolled fewer than 50 participants were excluded;; EPC = Evidence-based Practice Center; OA = osteoarthritis

Findings

The conclusions and SoE are summarized in Table A.

Key Question 1a: What is the clinical effectiveness of cell-based therapies, oral glucosamine and/or chondroitin, physical treatment interventions, weight loss, or home-based and self-management therapies in patients with OA of the knee, compared with appropriate placebo/sham controls or compared with other active interventions?

Key Question 1b: How do the outcomes of each intervention differ by the following population and study characteristics: sex, disease subtype (lateral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

Cell-Based Therapies

Four RCTs were identified that assessed short-term (4-12 weeks) and medium-term (12-26 weeks) effects of platelet-rich plasma (PRP) on pain and function.[13-16] We identified no RCTs on other cell-based therapies. These therapies were not reviewed in previous EPC SRs.

Key Points

- Among the cell-based therapies, only PRP was assessed in RCTs that met inclusion criteria for this review.
- A low strength of evidence based on four RCTs supports a beneficial effect of PRP on medium-term pain and quality of life.
- A low strength of evidence based on three RCTs supports a beneficial effect of PRP on medium-term quality of life.
- Evidence was insufficient to draw conclusions regarding the effects of PRP on medium-term function.
- Evidence was insufficient to draw conclusions regarding outcomes at shorter or longer times.

Glucosamine With or Without Chondroitin or Chondroitin Alone

Seven studies that assessed the effects of glucosamine,[17-19] chondroitin,[17, 18, 20, 21] or the combination met inclusion criteria.[17, 18, 22, 23] No studies addressed short-term outcomes of glucosamine combined with chondroitin, and no studies addressed short- or medium-term effects of glucosamine alone.

Key Points

- Glucosamine, chondroitin, and the combination of glucosamine plus chondroitin have shown somewhat inconsistent beneficial effects in large, multi-site placebo-controlled and head-to-head trials.

- Glucosamine + chondroitin: Three large, multi-site RCTs and one smaller RCT found low strength of evidence for a medium-term effect on pain and function but moderate strength of evidence for no long-term benefit on pain and function.
    - Two of three trials showed a medium-term benefit of glucosamine plus chondroitin on both pain and function (low strength of evidence).
    - A random effects pooled estimate for three studies showed no effect of long-term treatment on pain compared with control (pooled effect size -0.73, 95% CI −4.03; 2.57) (moderate strength of evidence).
    - A random effects pooled estimate for all three studies showed no effect of long-term treatment on function compared with control (pooled effect size -0.45, 95% CI −2.75; 1.84) (moderate strength of evidence).
- Glucosamine alone: No RCTs met inclusion criteria for short- or medium-term outcomes. Three RCTs that assessed effects of long-term glucosamine showed a moderate strength of evidence for no beneficial effects on pain and low strength of evidence for no benefit on function.
    - A random effects pooled estimate of three studies showed no effect of long-term glucosamine treatment compared with control on pain (n=1007; pooled effect size −0.05, 95% CI −0.22; 0.12; I^2 0%) (moderate strength of evidence)
    - Effects of long-term glucosamine on function showed no consistent benefit (low strength of evidence).
- Chondroitin alone: Three RCTs that assessed effects of chondroitin alone on pain and function showed inconsistent effects across time and outcomes.
    - Two large RCTs showed significant medium-term benefit of chondroitin alone for pain (low strength of evidence). Evidence was insufficient to assess medium-term effects on function.
    - Three large RCTs showed no long-term benefit of chondroitin alone on pain (moderate strength of evidence) or function (low strength of evidence).
- No studies were identified that compared glucosamine sulfate with glucosamine hydrochloride.
- No studies analyzed the time course of effects of glucosamine and/or chondroitin, but studies that examined effects at multiple time points showed that the maximum effects are achieved at 3 to 6 months.

Strength or Resistance Training

Ten studies that assessed strength or resistance training met inclusion criteria.[24-33]

Key Points

- It is unclear whether strength and resistance training have a beneficial effect on patients with OA of the knee. Pooled analyses support a nonstatistically significant benefit, and individual study findings suggest possible benefit on pain and function and significant benefit on total WOMAC scores.
- Strength and resistance training had no statistically significant beneficial effect on short-term pain or function based on pooled analyses of 5 RCTs but a significant short-term beneficial effect on the composite WOMAC total score based on 3 RCTs (low strength of evidence).

- Strength and resistance training showed a nonsignificant medium-term beneficial effect on function in a pooled analysis of 3 RCTs (low strength of evidence).
- Evidence was insufficient to assess long-term effects of strength and resistance training.
- No studies assessed the effects of any factors such as sex, obesity, or disease severity on outcomes of strength and resistance training.

Agility Training

Eight RCTs that assessed the effects of agility training met inclusion criteria.[26, 34-40]

Key Points

- It is unclear whether agility training alone has any benefit for patients with knee OA. Identified studies showed inconsistent effects across time points and outcomes.
- Agility training showed significant short-term beneficial effects on pain but not on function in 3 RCTs (low strength of evidence).
- Agility training showed no consistent beneficial effects on medium-term pain or function.
- Agility training showed no long-term beneficial effect on pain (3 RCTs) or function (2 RCTs) (low strength of evidence).

Aerobic Exercise

Five RCTs that assessed the effects of aerobic exercise met inclusion criteria.[41-45]

Key Points

- Based on five trials, aerobic exercise alone shows no long-term benefit on function; evidence was insufficient to draw conclusions regarding its effects on short- or medium-term outcomes or on long-term pain for patients with knee OA.
    - Evidence was insufficient to draw conclusions about short-term effects of aerobic exercise on pain, function, and total WOMAC scores (one RCT).
    - Evidence was insufficient to draw conclusions about medium-term effects of aerobic exercise on pain, function, and total WOMAC scores (two RCTs).
    - Evidence was insufficient to draw conclusions on effects of long-term aerobic exercise on pain (2 RCTs)
    - Aerobic exercise showed no significant long-term effects on function, based on three RCTs (low evidence).

General Exercise Therapy

Six interventions that combined exercise interventions and did not fit predefined categories were identified.[46-51]

Key Points

- General exercise programs appear to have beneficial medium-term effects on pain and function and long-term effects on pain for patients with knee OA, based on a relatively small number of heterogeneous RCTs.
    - Evidence was insufficient to assess the effects of general exercise therapy programs on short-term pain or function.
    - General exercise therapy programs had a beneficial effect on medium term pain and function, based on two RCTs (low strength of evidence).

- General exercise therapy programs showed beneficial long-term effects on pain, based on 4 RCTs (low strength of evidence), but evidence was insufficient to assess long-term effects on function or quality of life.

Tai Chi

Three RCTs that met inclusion criteria assessed the effects of tai chi compared with resistance training or no activity.[25, 52, 53]

Key Points

- Tai chi appears to have some short- and medium-term benefit for patients with OA of the knee, based on three small, short-term RCTs and one larger, 18-week RCT (total n=290).
  - Tai chi showed significant beneficial short-term effects on pain, comparable with those of conventional physical therapy, in one large RCT, but no significant effects in two small, brief RCTs (low strength of evidence).
  - Tai chi showed beneficial effects on short-term function compared with physical therapy and education but not compared with strength training, based on three RCTs (low strength of evidence).
  - Tai chi showed significant benefit for medium-term pain and function in 2 RCTs (low strength of evidence).
  - Evidence was insufficient to assess long-term effects of tai chi on pain, function, and other outcomes.

Yoga

One RCT that met inclusion criteria assessed the short-term effects of yoga.[54]

Key Points

- It is unclear whether yoga has any benefit for patients with OA of the knee, as we identified only one small RCT (n=36).

Manual Therapy (Including Massage and Acupressure)

Nine RCTs that assessed effects of manual therapy (including massage, self-massage, and acupressure) met inclusion criteria.[49, 51, 55-61]

Key Points

- It is unclear whether manual therapies have any benefit for patients with knee OA beyond the effects of exercise alone. Across nine RCTs, benefits were inconsistent across time points and outcomes. Pooled analysis showed no statistically significant effect on short term pain, although a clinically important effect could not be ruled out, due to the wide 95% confidence intervals.
- Manual therapy showed no statistically significant beneficial short-term effects on pain compared with treatment as usual, based on pooled analysis of three RCTs and four additional RCTs (low strength of evidence).
- Manual therapy showed no consistent beneficial effects on short-term function, based on four RCTs (low strength of evidence).
- Insufficient evidence was found to assess medium-term effects of manual therapy on pain, function, and other outcomes, based on four RCTs.

- Manual therapy had a small beneficial effect on long-term pain of borderline significance when combined with exercise, compared with exercise alone, based on two studies that conducted 12-month follow-up of three-month interventions (low strength of evidence).
- Evidence was insufficient to assess effects on long-term function.

Balneotherapy and Mud Treatment

Four RCTs that met inclusion criteria assessed the effects of balneotherapy, mud baths or topical mud.[62-65] No studies of balneotherapy assessed short- or long-term outcomes.

Key Points

- Balneotherapy had a beneficial effect on medium-term function, and a beneficial, but inconsistent effect on medium term pain across two single-blind RCTs (low strength of evidence). No studies assessed effects of balneotherapy on short- or long-term outcomes.
- Evidence was insufficient for an effect of mud (mud baths or topical mud) on short-term outcomes.

Heat, Infrared, and Therapeutic Ultrasound

One RCT that assessed the effects of heat,[66] one that assessed the effects of infrared,[67] and three that assessed the effects of pulsed and continuous U/S on outcomes of interest met inclusion criteria.[68-70] Only short-term effects were reported for heat and infrared, and no medium-term effects were reported for any of the interventions.

Key Points

- Insufficient evidence was identified to determine whether heat or infrared have any beneficial effects on any outcomes in patients with knee OA.
- Insufficient evidence was identified to determine whether continuous or pulsed therapeutic ultrasound (U/S) have beneficial effects on any outcomes.

TENS and NMES

Four RCTs that compared the effects of TENS with those of sham-TENS[71-74] and five RCTs that assessed the effects of NMES met inclusion criteria.[24, 75-78] No studies were identified that assessed long-term outcomes.

Key Points

- TENS showed a small but significant beneficial short-term effect on pain compared with sham controls based on pooled analysis of four RCTs (moderate strength of evidence), but no benefit for short-term function or other outcomes (low strength of evidence). The beneficial effect on pain was not sustained over the medium term.
- Evidence was insufficient to assess the short-term effects of NMES combined with exercise compared with exercise alone (or NMES compared with a sham control) on pain or function, based on three RCTs.
- Evidence was insufficient to assess the medium- and long-term effect of NMES on pain and function.

Pulsed Electromagnetic Field (PEMF)

Three RCTs that assessed short-term effects of PEMF on pain met inclusion criteria.[79-81] No RCTs were identified that assessed medium- or long-term outcomes of PEMF.

Key Points

- PEMF had a statistically nonsignificant beneficial effect on short-term pain based on a pooled analysis of three RCTs (low SoE).[79-81]
- Evidence is insufficient to assess the effects of PEMF on short-term function or other outcomes.

Whole-Body Vibration (WBV)

Seven RCTs that met the inclusion criteria assessed the effects of WBV on outcomes of interest.[82-88] No studies that assessed long-term effects were identified.

Key Points

- It is unclear whether WBV has a beneficial effect on patients with knee OA, as pooled analysis showed inconsistent effects on pain and function.
- WBV combined with exercise demonstrated no short-term beneficial effects on pain compared with exercise performed on a stable surface or not combined with WBV, based on three RCTs (low strength of evidence).
- Evidence is insufficient to draw conclusions on short-term effects of WBV on function or other outcomes.
- WBV-based exercise showed no beneficial medium-term effects on pain, based on pooled analysis of four RCTs (low strength of evidence).
- WBV-based exercise showed a small but statistically significant medium-term beneficial effect on WOMAC function, based on pooled analysis of 4 RCTs (n=180; SMD −0.26, 95% CI −0.45, 0.06) (low strength of evidence) that did not meet the MCID of -0.37. However no beneficial medium-term effect was observed on the 6-minute walk, based on pooled analysis of four RCTs (low strength of evidence).

Orthoses (Knee Braces, Shoe Inserts, Custom Shoes)

Three RCTs on knee braces,[89-91] eight RCTs on shoe inserts,[91-98] four RCTs on footwear,[99-102] and one RCT on cane use[103] met the inclusion criteria. No RCTs on short-term effects of footwear were identified.

Key Points

- It is unclear whether knee braces or other orthoses have a beneficial effect on patients with knee OA. Only a small number of RCTs on braces were identified, and studies of shoe inserts and specially designed shoes showed inconsistent effects across time points and outcomes.
- Knee Braces: Evidence was insufficient to determine whether custom knee braces had significant beneficial effects on any outcomes.
- Shoe Inserts showed no consistent beneficial effects across outcomes or follow-up times.

- Custom shoe inserts had no consistent beneficial short-term effects on pain (based on four RCTs), function (three RCTs), or WOMAC total scores (pooled analysis of three RCTs) (low strength of evidence).
- Shoe inserts showed no statistically significant beneficial effects on medium-term WOMAC pain (based on pooled analysis of three RCTs) or medium-term function (based on four RCTs) (low strength of evidence).
- Evidence was insufficient to determine long-term effects of shoe inserts on pain, but they showed no benefit for long-term function (low strength of evidence).

- Custom shoes: Evidence was insufficient to assess medium- or long-term effects on pain or function.
- Cane Use: Insufficient evidence exists to assess the benefit of cane use on pain, physical function, and quality of life.

Weight Loss

Five RCTs[104-108] and five single-arm trials (reported in six publications)[109-114] that assessed the effects of weight loss on OA met inclusion criteria.

Key Points

- Weight loss with or without exercise has a beneficial effect on medium-term pain and function and on long-term pain but inconsistent effects across studies on long-term function and quality of life.
  - Evidence was insufficient to assess short-term effects of dieting, with or without exercise on pain and function,.
  - Weight loss had a significant beneficial effect on medium-term pain, based on two RCTs and four single-arm trials. One single-arm trial assessed and reported a dose-response effect between weight and outcomes of interest (moderate-level evidence).
  - Weight loss had a significant beneficial effect on medium-term function, based on two RCTs and three single-arm trials (low strength of evidence).
  - Weight loss had a significant long-term beneficial effect on pain based on three RCTs and one single-arm trial (low level of evidence) but inconsistent effects on function and quality of life, based on two RCTs (low strength of evidence).

Home-Based and Self-Management Interventions

Five RCTs that met inclusion criteria assessed the effects of home-based exercise programs or self-management programs.[26, 29, 44, 108, 115]

Key Points

- A home-based exercise program and a self-management plus exercise program showed significant beneficial short-term effects on pain, based on two RCTs (low strength of evidence).
- Evidence was insufficient to assess the effects of home-based and self-management programs on short-term function but self-management programs had significant beneficial effects on medium-term function compared with control conditions (low strength of evidence.
- Self-management and PCST plus strength training showed beneficial medium-term effects on pain, based on three RCTs (low strength of evidence).

- Evidence was insufficient to assess the medium-term effects of self-management programs on quality of life.
- Evidence was insufficient to assess the long-term effects of self-management on pain or function.

Key Question 2a: What harms are associated with each intervention in patients with OA of the knee?

Key Question 2b: How do the harms associated with each intervention differ by the following population or study characteristics: sex, disease subtype (lateral tibiofemoral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

Key Findings and SoE for Key Question 2a-b

- Of 57 studies that described some assessment of adverse events (AEs), 18 studies reported on serious adverse events (SAEs). Most reported only whether any SAEs were identified. SAEs were extremely rarely reported and not limited to active treatment groups. AEs are shown by study in Appendix H of the full report.
- No studies assessed differences in adverse events by characteristics of subpopulation.

Discussion

The purpose of this report was to update the findings of a 2007 EPC SR on the effects of supplements containing glucosamine with or without chondroitin, the findings of a 2012 EPC SR on the effects of interventions within the physical therapy scope of practice, and several newer interventions (cell-based therapies) on clinical outcomes in patients with knee OA. The population of interest for this review consists of patients with a documented diagnosis of OA of the knee.

Summary of Findings in Relationship to What Is Already Known

Table B compares the findings of the current review with those of the 2007 and 2012 reviews as well as several additional recent systematic reviews.

Implications for Clinical and Policy Decisionmaking

OA of the knee is an increasingly prevalent, progressively debilitating condition. Decisions regarding therapies for OA of the knee depend on a number of factors. Patient preferences have the strongest influence and are based on a combination of pain and perceived functional limitations and their influence on quality of life. Treatments for the condition range from the most minimal and least invasive (dietary supplements and over-the-counter analgesics) to total

knee replacement. The current report considered only a subset of available interventions, and all fell along the less invasive end of the continuum.

A number of the interventions assessed in the report showed short- or medium-term benefit but either were not assessed sufficiently over the long term (meaning after a long intervention or after a shorter intervention with a long follow-up time, e.g., tai chi, TENS, or PRP) or showed minimal benefits in the long term (e.g., glucosamine chondroitin). Several interventions showed beneficial long-term effects, including weight loss and several forms of physical activity (e.g., general exercise programs of the type taught by physical therapists). Because of study design and the numbers and duration of studies, it is not clear which physical activities are most effective, whether they are most effective in combination, or if benefit depends entirely on the individual patient. Adherence, which is obviously an important factor, was seldom assessed in the studies that met inclusion criteria.

One intervention that showed some medium-term benefit, intraarticular injection of PRP, has undergone limited testing for OA of the knee, especially regarding the effects of repeated injections. In addition, this intervention may not currently be covered by most insurers and its use as an intraarticular injection is considered off label by the FDA.

Pending longer RCTs of therapies that show promise for benefits in the short term, the implementation of progressive treatment plans, guided entirely by patient preference is supported by the findings of this review.

Limitations of the Evidence Base

Limitations due to study quality. The results of the RoB assessments for each study appear in Table F1 in Appendix F of the report. In the Results section of the full report, we have provided summary RoB scores for each study. The most prevalent limit to study quality was participant blinding: Only 33 of 85 RCTs reported an attempt to blind participants appropriately, using sham injections, placebo pills, sham applications of a treatment such as TENS, or in the case of exercise interventions, a control condition that could be considered an intervention itself. Many RCTs of physical interventions reported that participants were not or could not be blinded. Although outcome assessors were often reported to have been blinded in these studies, many of the outcomes of interest to this report were self-assessed (such as pain and WOMAC function). This lack of blinding significantly limits conclusions we can draw from the literature and is further discussed below in regard to comparators.

Another quality issue is the large number of RCTs for which adequate concealment of allocation could not be ascertained: 46 of 85. The inability to ascertain allocation concealment might sometimes be attributed to word limitations in publications, but is still a concern.

A third quality concern is the finding that 41 studies did not indicate use of intent-to treat analysis; since participants who are not experiencing benefit from treatment are more likely to drop out before study completion, per protocol analysis could artificially inflate apparent effects.

Fourth, 31 RCTs indicated evidence of incomplete adherence. This figure is actually deceptively low, as most interventions involving exercise require that participants work out on their own on days when they are not being supervised. Most studies did not attempt to monitor offsite compliance, and no studies assessed the effect of such compliance or adherence on outcomes.

Finally, although most studies demonstrated that participants were similar at baseline, some similarities were not routinely considered, such as weight status, or disease stage or severity, and almost no studies stratified outcomes by any baseline characteristics.

Additional limitations. A variety of additional limitations were also identified in the literature:

- Limited applicability of studies conducted in an academic setting and enrolling highly motivated participants.
- Failure to report compliance or adherence to interventions.
- Omission of information on sources, purity, and concentrations of dietary supplements and/or use of preparations not available commercially, as well as use of proprietary preparation processes for PRP.
- Use of— or failure to adequately control for—multicomponent interventions, including failure to exclude or account for use of rescue analgesics or other treatments.
- Short duration of interventions and follow-up, given the progressive, chronic nature of the condition. Although studies with a minimum follow-up of less than four weeks were excluded, we did not consider the duration of an intervention as an inclusion criterion (as interventions such as PRP injection have no duration). Thus, the interval between the end of an intervention and outcome assessment, especially medium- or long-term follow-up, differed across studies.
- Lack of sufficient numbers of studies with similar interventions to enable assessment of the effects of dose (or intensity, frequency, and duration of physical activity sessions). A 2015 Cochrane review found no evidence for significant differences in the effects of low vs. high intensity interventions on knee or hip OA patients but regarded that the evidence was insufficient to draw firm conclusions.[116]
- Selection of appropriate study comparators, particularly given the self-reported, subjective nature of pain as an outcome. For the current report, we excluded studies that used only comparators of unclear efficacy (e.g., HA as a comparator for PRP) to make it possible to discern the magnitude of the placebo effect. We also excluded studies that used a participant's less-painful knee as the comparator. Many of the studies we included employed usual care as a control; however, usual care often included a physical therapy program (usually some combination of strength and agility exercises and manipulation). Therefore, a lack of effect might simply reflect the limits of possible improvement over that from standard physical therapy. This conclusion is particularly likely, given that most studies that reported no differences in outcomes between interventions and active controls did report significant improvements from baseline. The most appropriate control for studies of physical interventions remains unclear.
- Limited measurement or reporting of a number of outcomes of interest, e.g., quality of life and TKR.
- Small sample size.
- Heterogeneity with regard to interventions, comparators, outcome measures, durations of treatment and follow-up, and even reporting of the scales used for some outcome measures, all of which limited pooling.
- Challenges that largely precluded assessing the clinical as well as the statistical significance of any beneficial findings that is, assessing whether statistically significant outcomes met a prespecified minimum clinically important difference (MCID). First, some publications failed to include the numerical scales used with their assessment tools, making it impossible to assess the potential clinical

significance of findings. Second, published MCIDs depend on the disease severity of the participants; the included studies often did not report or varied widely in the disease severity of participants. We selected and applied one set of values that has been applied in a number of similar reviews[117] to the small number of statistically significant outcomes for which we had pooled standardized mean differences or for which we were able to identify the numerical measurement scales. But, thirdly, it is important to note that MCIDs are derived by translating patients' responses on a scale of multiple items (e.g., the full WOMAC scale contains 24 items), each item graded using numerical rating scales of 4-100 points, to their response to a smaller, subjective set of anchoring questions; thus, their validity continues to be debated. Further, in studies with continuous outcomes, even if the mean difference is less than the MCID, a proportion of participants experience outcomes that exceed the MCID. Thus rigorously applying the MCID could prevent patients from obtaining potentially effective treatments.

Future Research Recommendations

In general, future studies need to enroll sufficient numbers of participants to enable prespecified subgroup analysis according to important participant characteristics and to enable assessment of both statistical and clinical improvement. Studies also need to employ designs that permit assessing the effects of specific interventions and to consider including both active (sham) and passive comparison groups to enable participant blinding. Isolation of the interventions being assessed needs to be accomplished both by careful design of the interventions themselves and by prohibiting participants from using alternative modes of therapy. In addition, many interventions need to be conducted for longer durations and mechanisms need to be developed to better measure compliance. Reported outcomes need to include the percent of participants who experience improvement as well as an estimate of whether the effect size achieves a MCID. In addition, the use of imaging and other nonclinical measures will help clarify structure-function relationships and outcomes of interventions.

Recent OARSI guidelines on design of clinical trials for knee OA therapies include 25 recommendations. Among them are clear definition (of and rational for) inclusion/exclusion criteria; assessment and reporting of disease severity; ensuring randomization, blinding (to the extent possible), and similarity of important characteristics at baseline; use of validated outcome measures and steps to minimize bias in patient-reported outcomes.[118] Recommendations specific to particular interventions are described below.

Cell-based therapies. Based on our finding of a significant effect of PRP in a small number of small, high RoB studies, and the number of studies that did not meet inclusion criteria because they compared PRP only to HA, we believe a large, saline-controlled trial is needed. Although corticosteroids could provide an additional comparator for noninferiority, the immediate adverse effects of intraarticular injection of corticosteroids would be impossible to mask. Residual benefits that remain after the intervention is discontinued (and the effect of follow up treatment) also need to be assessed.

In addition, no studies of stem-cell therapy or other cell-based therapies met inclusion criteria. A large multisite commercial clinic that was contacted for trial results did not respond to the request. Clinicaltrials.gov lists several registered trials of stem-cell treatments for OA of the knee, which should be monitored for published findings. We also identified four published studies of gene therapies (using autologous chondrocytes genetically modified to deliver a

growth factor and designed to be injected intraarticularly), which to date, have been tested only in Phase II trials.[119-122]

Glucosamine with or without chondroitin. The 2016 MOVES Trial found significant beneficial medium-term effects on pain, function, stiffness, and quality of life for a prescription form of glucosamine hydrochloride plus chondroitin that were comparable with those of a Cox-2 inhibitor in a large patient population with severe pain. The rate of AEs was relatively small and similar across groups (individuals with cardiovascular conditions were excluded). Thus far, longer-term outcomes have not been reported but would need to be considered in formulating guidelines regarding the use of a prescription grade form of the supplement, especially in light of the findings of the LEGS Trial that glucosamine, chondroitin, and the combination had no beneficial effects at 1 and 2 years compared with placebo. In addition, a head-to-head trial similar to MOVES should be conducted using a combination of glucosamine sulfate and chondroitin, as some evidence has suggested glucosamine sulfate is more effective than glucosamine hydrochloride.

Physical interventions. The studies on strength, agility, and aerobic training that met inclusion criteria usually combined the training modality that was being tested with additional exercises, for example, a strength training intervention would include aerobic exercise as a warm-up and would sometimes include a brief session of exercises aimed at improving agility or gait as well. This design matches the physical therapy regimens in current use and probably makes sense as a therapeutic regimen, but it requires that studies that aim to test a specific modality are carefully designed to ensure that the results can be attributed to the intervention being tested. Other SRs have also noted the difficulty in drawing conclusions regarding the clinical utility of various physical interventions.

Studies are needed to assess the effects of varying the "dose" of physical interventions, by comparing different numbers, durations, and/or intensities of treatments.

The efficacy of individually tailored multicomponent interventions also needs to be assessed but traditional clinical trial methods may not be well-suited to assess such interventions, because testing custom interventions essentially requires that patients serve as their own controls. A number of the trials included in our review modified interventions based on an assessment of individual participant deficits but only one assessed the effects of doing so and found no differences from participants who received a nontailored therapy.

Only one study of aquatherapy, and few studies of yoga or tai chi, met inclusion criteria. Larger trials of these interventions alone compared with both active comparators (to mask the intervention of interest) and waiting list (or other passive) comparators are needed, as they can easily be undertaken by sedentary individuals with no prior training.

OARSI recently published guidelines for the design and conduct of clinical trials of rehabilitation interventions, which include the physical interventions.[118, 123] Recommendations are similar to those of the OARSI guidelines for assessing interventions for OA of the knee.[118] Emphasis is on participant blinding when possible; assessor blinding; use of both sham (active) and passive comparators; description of baseline severity (with clinical measures, if desired); prespecification of adverse events for assessment; use of valid outcome measures with a benchmark, if possible; and assessment of the percent of participants who achieve improvement. Comparative effectiveness trials are advocated for testing novel treatments against those with established effectiveness or when blinding is not otherwise possible. Caution is suggested in applying published MCIDs, as they have been shown to differ by population and other factors.[124]

Weight loss. This review showed beneficial effects of weight loss interventions on pain and function. Future studies need to clarify the roles of exercise and self-efficacy education in the observed effect to assess whether exercise and/or self-efficacy have their own effects, independent of caloric restriction and weight loss or if these co-interventions assist with weight loss and weight maintenance.

The OARSI recently released guidelines on design and conduct of diet and exercise interventions for OA.[123] Most of the recommendations were similar to those provided for rehabilitation and for OA of the knee interventions in general, in copublications. However, they also provided several additional noteworthy recommendations. These include the need to determine in Phase 1 trials whether high-intensity strength training, aimed at increasing /quadriceps muscle strength, is safe in older adults with knee OA. Also recommended is allowing monitored use of rescue medication (analgesics), as weight loss trials tend to be longer in duration than other studies.

Home-based therapies. Our results, based on only a small number of studies, suggest home-based therapies with periodic supervision show beneficial effects on pain and function. This model has the advantage of requiring few clinic visits but the disadvantages of lack of monitoring of compliance and correct form when performing activities. The 2016 SR of home-based therapies by Anwer and colleagues also cites the issue of difficulty assessing compliance with home-based interventions.[125] Future research studies of home-based exercise could easily employ any one of a number of fitness monitoring devises to assess adherence and could use applications like Skype to periodically monitor performance.

Adverse effects. Future studies need to prespecify AEs of concern. Researchers need to actively and systematically collect information on adverse effects of interventions at defined intervals, particularly for cell-based therapies and intensive exercise programs.

Conclusions

Among the interventions assessed in this report, many had insufficient evidence to determine their benefit for managing OA of the knee. Interventions that show beneficial effects on short-term outcomes of interest include TENS (moderate strength of evidence [SoE]), agility training, home-based programs, and PEMF on pain (low SoE); tai chi on pain and function; and strength and resistance training on WOMAC total scores (low SoE).

Interventions that show beneficial effects on medium-term outcomes include weight loss for pain (moderate SoE) and function, intraarticular platelet-rich plasma on pain and quality of life, glucosamine plus chondroitin on pain and function, chondroitin sulfate alone on pain, general exercise programs on pain and function, tai chi on pain and function, whole-body vibration on function, and home-based programs on pain and function (low SoE).

Interventions that show beneficial long-term effects include agility training and general exercise programs for pain and function, and manual therapy and weight loss for pain (low SoE). A moderate SoE supports a lack of long-term benefit of glucosamine-chondroitin on pain or function, and glucosamine or chondroitin sulfate alone on pain. Insufficient evidence was found for long-term effects, and for additional outcomes, such as stiffness, swelling, quality of life, and avoidance of knee replacement for most interventions.

Larger randomized controlled trials are needed, with more attention to appropriate comparison groups and longer duration, to assess newer therapies and to determine which types of interventions are most effective for which patients.

Table A. Summary strength of evidence

Intervention/ Follow-up	Pain	Function	WOMAC Total	Quality of Life	Other
Platelet-rich plasma					
Short-term	I (2)	I (2)	I(2)	I(1)	
Medium-term	⇧**L** (4)	I	I(2)	⇧**L**(3)	
Long-term	I (0)	I (0)		I (0)	
Glucosamine with or without chondroitin					
Glucosamine plus chondroitin					
Short -term	I(0)	I(0)		I(0)	
Medium-term	⇧**L(3)***	⇧**L(3)***		NR	
Long-term pain	⇩M (3)[#]	⇩M(3)[#]			
Glucosamine					
Short-term	I(0)	I(0)		I(0)	
Medium-term	I(0)	I(0)		I(0)	
Long-term	⇩M (3)	⇩M (3)			TKR risk ⇧**L(2)**
Chondroitin-sulfate					
Short-term	I(1)	I(1)		I(1)	
Medium-term	⇧**L(2)**	I(2)		I(0)	
Long-term	⇩M (3)	⇩L (2)		I(0)	
Aerobic Exercise					
Short-term	I(1)	I(1)	I(1)		
Medium-term	I(2)	I(2)	I(1)		
Long-term	I(2)	⇩L (3)			
Strength/resistance Training					
Short-term	⇩L(5)[#]	⇩L(5)[#]	⇧**L(3)**		
Medium-term	I(2)	⇩L(3)[#]	I(2)		
Long-term	I(1)	I(1)	I(1)		
Agility Training					
Short-term pain	⇧**L(3)** †	⇩L (3)	I(1)		
Medium-term	⇩L (3)	⇩L (3)			
Long-term	⇧**L(3)**	⇧**L(2)**			
General Exercise					
Short-term	I(1)	I(1)	⇩L (2)	⇩L (2)	
Medium-term	⇧**L(2)**	⇧**L(2)**			
Long-term	⇧**L(3)**	I(2)	I(2)	⇩L (3)	TUG, ⇧L(3)
Tai Chi					
Short-term	⇧**L(3)**	⇧**L(3)**			
Medium-term	⇧**L(2)**	⇧**L(2)**			
Long-term	I(1)	I(1)			
Yoga					
Short-term	I(1)				
Manual Therapy					

Intervention/ Follow-up	Pain	Function	WOMAC Total	Quality of Life	Other
Short-term	⇩L(3)[#]	⇩L (4)	I(4)		
Medium-term	I(4)	I(4)	⇩L(3)		
Long-term	⇧**L(2)**	I(0)	I(1)		
Balneotherapy and Mud Therapy					
Balneotherapy					
Short-term	I(0)	I(0)			
Medium-term pain	⇧**L(2)**	⇧**L(2)**			
Topical Mud therapy					
All durations	I(0)	I(0)			
Mud bath therapy					
All durations	I(0)	I(0)			
Heat, Infrared Ultrasound					
Heat or infrared					
All durations	I(3)	I(3)	I(3)		
Ultrasound					
Short-term	I(2)	I(1)	I(1)		
Medium-term	I(1)	I(1)			
Long-term	I(1)	I(1)			
Pulsed Electromagnetic Field					
Short-term	⇧**L(3)**[#]	I(1)	I(1)		
Medium-term	I(0)	I(0)			
Long-term	I(0)	I(0)			
Transcutaneous Electrical Nerve Stimulation (TENS)					
Short-term	⇧**M(4)**[ǂ]	⇩L (3)	⇩L (3)		
Medium-term	⇩L(2)	⇩L(2)	I(1)		
Long-term	I(0)	I(0)			
Neuromuscular Electrical Stimulation (NMES)					
Short-term	I(2)	I(0)			
Medium-term	I(2)	I(0)			
Whole-body Vibration(WBV)					
Short-term	⇩L(3)	I(1)	I(2)	I(1)	I(3)
Medium-term	⇩L(4)[#]	**⇧L(4)**[#ǂ]			⇩L(4)[#] 6' walk
Orthoses (Braces, Shoe Inserts, and Custom Shoes)					
Braces					
Short-term	I(1)	I(0)			
Medium-term	I(1)	I(0)			
Long-term	I(1)	I(0)			
Shoe inserts					
Short-term	⇩L(4)	⇩L(3)	⇩L(3)[#]		
Medium-term	⇩L(3)[#]	⇩L(4)	I(1)		
Long-term	I(2)	I(2)			
Custom Shoes					

Intervention/ Follow-up	Pain	Function	WOMAC Total	Quality of Life	Other
Short-term	I(0)	I(0)			
Medium-term	I(2)	I(1)	I(1)		
Long-term	I(1)	I(0)			
Cane					
Short-term	I(1)	I(1)	I(1)		
Weight loss					
Short-term	I(2)	I(2)			
Medium-term pain	**⇧M(6)****	**⇧L(6)****	I(1)		
Long-term	**⇧L(4)****	I(2)	I(1)		
Home-based and Self-Management Programs					
Short-term	**⇧L(2)**	I(2)	**⇧L(2)**		
Medium-term	**⇧L(3)**	**⇧L(4)**	I(1)		I(2)
Long-term	I(1)	I(2)		I(1)	I(1)
Key Question 2 Adverse Events					⇩M SAEs and nonSAEs

Table Notes: Blank spaces=outcome not reported; Bold-face text=low- or moderate strength of evidence; ⇧=beneficial effect; ⇩=no beneficial effect; L=low strength of evidence; M=moderate strength of evidence; I=insufficient evidence; (n)=number of trials that met inclusion criteria; TKR=total knee replacement risk; *Beneficial effect vs. analgesic or placebo; #Pooled analysis; †compared with placebo but not strength training; ₴Did not meet MCID; **RCTs and single-arm trials.

Table B. Findings in relation to what is already known

Intervention	Prior Findings	Findings of the Current Review
Platelet Rich Plasma	Several 2015 SRs reviewed the effects of PRP with mixed findings, however all prior reviews included studies comparing PRP to hyaluronic acid or corticosteroid injections	Beneficial short-term effects compared with saline controls
Glucosamine and/or chondroitin	The 2007 EPC review identified no significant benefit for glucosamine and/or chondroitin compared with placebo based on one large RCT (GAIT Trial)	**Glucosamine plus chondroitin**: Large noninferiority trial found comparable short-and medium-term effects for glucosamine plus chondroitin compared with NSAIDs, but no long-term effects of either. This trial did not include a placebo control. The 2008 post hoc analysis conducted by the authors of the GAIT trial found that when participants were stratified by baseline pain, those with moderate to severe pain demonstrated a trend toward improvement from glucosamine plus chondroitin (proportion experiencing 20 percent or greater improvement in pain).[126] The effect was moderated by the large placebo response. **Glucosamine alone**: No new trials assessed short- or medium-term effects; three RCTs found no consistent long-term effects on outcomes of interest. **Chondroitin alone**: Evidence of medium-term effects but no long-term effects, in three new trials and a long-term follow-up of the GAIT trial. The analysis also found that the effect of chondroitin on swelling was seen predominantly in those with less-advanced disease
Strength and Resistance Training	The 2012 SR found low-level evidence that "strengthening exercise" decreased pain and improved several other outcomes among individuals with OA of the knee, but no evidence for improvement in function was supported (no definition of criteria for categorizing interventions)	Evidence for a significant beneficial effect on total WOMAC scores and a nonstatistically significant beneficial effect on short-term pain and function based on pooled analysis of five RCTs, strengthening the findings of the 2012 EPC review on beneficial effects of strength and resistance training on pain. An ongoing study is testing effects of intensity and duration (START,ClinicalTrials.gov NCT01489462)
Agility Training	The 2012 report found beneficial effects on long-term pain.[11]	Low-strength evidence from six RCTs that strengthened the findings of the 2012 report and provides evidence on short-term benefits for pain (low strength of evidence).
Tai Chi	The 2012 report found evidence from two studies	Low-strength evidence supporting a beneficial effect of

Intervention	Prior Findings	Findings of the Current Review
	supporting benefits of tai chi for a composite measure of function but not pain, quality of life, or other measures of function.	Tai chi on short-and medium-term pain and function
Yoga	The 2012 review identified no RCTs. A 2016 SR on the effects of yoga on OA of the knee found a significant short-term effect on pain; this review included six studies, some with very short follow-up times.[127]	Insufficient new evidence to draw conclusions.
Manual Therapy	The 2012 SR reported a low strength of evidence for an effect of massage on function based on two pooled studies (6-13 weeks) and reported improvements in disability and other outcomes based on three unpooled studies.	Low-strength evidence for a lack of beneficial effect of mixed methods of manual therapy on short-term pain, based on three pooled RCTs, but no consistent effects on medium-term pain, function, or other outcomes.
WBV	The 2012 SR did not consider WBV as an intervention, and no other recent high-quality SRs assessed the effects of WBV on pain or function.	A significant beneficial effect of WBV on medium-term function but not on medium-term pain. Insufficient evidence was found for short- and long-term effects
TENS and NMES	The 2012 SR identified a beneficial effect of electrical stimulation, (including TENS and NMES) on short-term pain, based on meta-analysis of seven RCTs, but no other significant effects of electrical stimulation.	TENS: A beneficial short-term effect of TENS on pain (moderate-level evidence), but no effects of TENS on function and no medium- or long-term effects. NMES: Insufficient evidence to draw conclusions regarding the effects of NMES on pain or function; strength, which is considered the primary outcome for NMES, was not included as an outcome of interest in the current study,
Orthoses	The 2012 SR identified low-level evidence for a beneficial effect of foot orthoses on function. They did not identify studies on use of knee braces, custom shoes, or cane use. A 2015 Cochrane update review assessed the efficacy of orthoses (including one type of shoe, a custom variable-stiffness shoe) and knee braces.[128] That review included only one RCT that was published since the 2012 SR (included in the current review) and, in agreement with the current review, concluded that braces and orthoses had no consistent effects on pain or function	Foot orthoses (shoe inserts): No beneficial effects. No evidence for beneficial effects of knee braces, custom shoes, or canes on pain or function.
Therapeutic ultrasound	The 2012 review found beneficial effects of ultrasound on pain and one composite function measure, but not on other measures of function.	Insufficient evidence on effects.
PEMF	The 2012 review found beneficial effects on global	A small, nonstatistically significant benefit for short-

Intervention	Prior Findings	Findings of the Current Review
	assessment but no effects on pain, function, or other outcomes.	term pain.
Heat, infrared	The 2012 review found beneficial effects of heat on quality of life and one measure of function but not on pain or other function outcomes.	Insufficient evidence on the effects of heat or infrared therapy
Balneotherapy, mud therapy, aquatic exercise	The 2012 review did not include balneotherapy or mud therapy. The review identified a beneficial effect of aquatic exercise on disability but not on pain or other function outcomes.	Beneficial effects of balneotherapy on medium term pain and function but insufficient evidence on mud therapy or aquatic exercise
Weight Loss	Earlier EPC reports did not assess the effects of weight loss on knee OA.	Significant benefit for medium- and long-term outcomes.
Home-based and self-management interventions	The 2012 review did not assess the effects of these interventions separately from the kinds of exercises they included.	Evidence for significant beneficial effects of these interventions on short term pain and medium-term pain and function.
Adverse Events	The 2007 SR reported that, in general, AEs for glucosamine with or without chondroitin did not differ between treatment and placebo groups, and no SAEs were reported. Likewise, the 2012 SR on physical interventions reported that AEs did not differ significantly between treatment and control groups and did not deter individuals from continued participation in trials.	No difference in AEs between glucosamine and/or chondroitin and placebo or active controls. PRP was associated with pain and stiffness that increased with the number of injections. Weight loss diet interventions associated with higher proportions of nonserious gastrointestinal events No differences were seen between active and control groups in reported AEs for other interventions,

Table Notes: AE=adverse event; EPC=Evidence-based Practice Center; GAIT=Glucosamine/Chondroitin Intervention Trial; NMES=neuromuscular electrical stimulation; OA=osteoarthritis; PEMF=pulsed electromagnetic field; PRP=platelet-rich plasma; RCT=randomized controlled trial; SAE-serious adverse event; SR=systematic review; TENS=transcutaneous electrical nerve stimulation; WBV=whole body vibration.

References

1. Samson DJ, Grant MD, Ratko TA, et al. Treatment of primary and secondary osteoarthritis of the knee. Evidence Report/Technology Assessment No. 157 (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-02-0026) Agency for Healthcare Research and Quality. Rockville, MD: September 2007.

2. Schiphof D, de Klerk BM, Kerkhof HJ, et al. Impact of different descriptions of the Kellgren and Lawrence classification criteria on the diagnosis of knee osteoarthritis. Ann Rheum Dis. 2011 Aug;70(8):1422-7. doi: ard.2010.147520 [pii]10.1136/ard.2010.147520. PMID: 21555325.

3. Cibere J, Zhang H, Thorne A, et al. Association of clinical findings with pre-radiographic and radiographic knee osteoarthritis in a population-based study. Arthritis Care Res (Hoboken). 2010 Dec;62(12):1691-8. doi: 10.1002/acr.20314. PMID: 20665737.

4. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012 Apr;64(4):465-74. PMID: 22563589.

5. American Academy of Orthopaedic Surgeons. Treatment of Osteoarthritis of the Knee, 2nd Edition: SUMMARY OF RECOMMENDATIONS. http://www.aaos.org/research/guidelines/OAKSummaryofRecommendations.pdf.

6. Newberry SJ, FitzGerald JD, Maglione M, et al. Systematic Review for Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee. (Prepared by the Southern California Evidence-based Practice Center). Technology Assessment Report. AHRQ. Project ID: DJDTO913.

7. Shamliyan TA, Wang SY, Olson-Kellogg B, et al. Physical Therapy Interventions for Knee Pain Secondary to Osteoarthritis. Rockville (MD): Agency for Healthcare Research and Quality; 2012.

8. Chou R, McDonagh MS, Nakamoto E, et al. Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review. Comparative Effectiveness Review No. 38. (Prepared by the Oregon Evidence-based Practice Center under Contract No. HHSA 290 2007 10057 I) Agency for Healthcare Research and Quality. Rockville, MD: October 2011.

9. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2014. p. Chapters available at: www.effectivehealthcare.ahrq.gov.

10. Osteoarthritis of the Knee. Draft Key Questions. Rockville, MD: AHRQ Effective Health Care Program; 2015. http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displaytopic&topicid=633. Accessed on March 7 2016.

11. Shamliyan TA, Wang SY, Olson-Kellogg B, et al. AHRQ Comparative Effectiveness Reviews. Physical Therapy Interventions for Knee Pain Secondary to Osteoarthritis. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012.

12. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol. 2014;14:25. doi: 10.1186/1471-2288-14-25. PMID: 24548571.

13. Patel S, Dhillon MS, Aggarwal S, et al. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Med. 2013

Feb;41(2):356-64. doi: 10.1177/0363546512471299. PMID: 23299850.

14. Gormeli G, Gormeli CA, Ataoglu B, et al. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. Knee Surg Sports Traumatol Arthrosc. 2015 Aug 2doi: 10.1007/s00167-015-3705-6. PMID: 26233594.

15. Rayegani SM, Raeissadat SA, Taheri MS, et al. Does intra articular platelet rich plasma injection improve function, pain and quality of life in patients with osteoarthritis of the knee? A randomized clinical trial. Orthop Rev (Pavia). 2014 Aug 8;6(3):5405. doi: 10.4081/or.2014.5405. PMID: 25317308.

16. Acosta-Olivo C, Esponda-Colmenares F, Vilchez-Cavazos F, et al. Platelet rich plasma versus oral paracetamol for the treatment of early knee osteoarthritis. Preliminar study. Cirugia y Cirujanos. 2014;82(2):163-9.

17. Sawitzke AD, Shi H, Finco MF, et al. Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. Ann Rheum Dis. 2010 Aug;69(8):1459-64. doi: 10.1136/ard.2009.120469. PMID: 20525840.

18. Fransen M, Agaliotis M, Nairn L, et al. Glucosamine and chondroitin for knee osteoarthritis: A double-blind randomised placebo-controlled clinical trial evaluating single and combination regimens. Annals of the Rheumatic Diseases. 2014;6.

19. Bruyere O, Pavelka K, Rovati LC, et al. Total joint replacement after glucosamine sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients from two previous 3-year, randomised, placebo-controlled trials. Osteoarthritis Cartilage. 2008 Feb;16(2):254-60. doi: 10.1016/j.joca.2007.06.011. PMID: 17681803.

20. Zegels B, Crozes P, Uebelhart D, et al. Equivalence of a single dose (1200 mg) compared to a three-time a day dose (400 mg) of chondroitin 4&6 sulfate in patients with knee osteoarthritis. Results of a randomized double blind placebo controlled study. Osteoarthritis Cartilage. 2013 Jan;21(1):22-7. doi: 10.1016/j.joca.2012.09.017. PMID: 23059756.

21. Kahan A, Uebelhart D, De Vathaire F, et al. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2009 Feb;60(2):524-33. doi: 10.1002/art.24255. PMID: 19180484.

22. Hochberg MC, Martel-Pelletier J, Monfort J, et al. Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: A multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. Annals of the Rheumatic Diseases. 2016;75:37-44. PMID: 2015073670 FULL TEXT LINK http://dx.doi.org/10.1136/annrheumdis-2014-206792.

23. Bellare N, Argekar H, Bhagwat A, et al. Glucosamine and chondroitin sulphate supplementation along with diet therapy provides better symptomatic relief in osteoarthritic patients as compared to diet therapy alone. International Journal of Pharmaceutical Sciences Review and Research; 2014. p. 215-23.

24. Bruce-Brand RA, Walls RJ, Ong JC, et al. Effects of home-based resistance training and neuromuscular electrical stimulation in knee osteoarthritis: a randomized controlled trial. BMC Musculoskelet Disord. 2012;13:118. doi: 10.1186/1471-2474-13-118. PMID: 22759883.

25. Wortley M, Zhang S, Paquette M, et al. Effects of resistance and Tai Ji training on mobility and symptoms in knee

osteoarthritis patients. Journal of Sport and Health Science; 2013. p. 209-14.

26. Rogers MW, Tamulevicius N, Semple SJ, et al. Efficacy of home-based kinesthesia, balance & agility exercise training among persons with symptomatic knee osteoarthritis. J Sports Sci Med. 2012;11(4):751-8. PMID: 24150088.

27. Oliveira AM, Peccin MS, Silva KN, et al. Impact of exercise on the functional capacity and pain of patients with knee osteoarthritis: a randomized clinical trial. Rev Bras Reumatol. 2012 Dec;52(6):876-82. PMID: 23223698.

28. Nam CW, Kim K, Lee HY. The influence of exercise on an unstable surface on the physical function and muscle strength of patients with osteoarthritis of the knee. J Phys Ther Sci. 2014 Oct;26(10):1609-12. doi: 10.1589/jpts.26.1609. PMID: 25364125.

29. Bennell KL, Ahamed Y, Jull G, et al. Physical therapist-delivered pain coping skills training and exercise for knee osteoarthritis: Randomized controlled trial. Arthritis Care Res (Hoboken). 2015 Sep 28doi: 10.1002/acr.22744. PMID: 26417720.

30. Foroughi N, Smith RM, Lange AK, et al. Progressive resistance training and dynamic alignment in osteoarthritis: A single-blind randomised controlled trial. Clin Biomech (Bristol, Avon). 2011 Jan;26(1):71-7. doi: 10.1016/j.clinbiomech.2010.08.013. PMID: 20869141.

31. Imoto AM, Peccin MS, Trevisani VF. Quadriceps strengthening exercises are effective in improving pain, function and quality of life in patients with osteoarthritis of the knee. Acta Ortop Bras. 2012;20(3):174-9. doi: 10.1590/s1413-78522012000300008. PMID: 24453599.

32. Jorge RTB, de Souza MC, Chiari A, et al. Progressive resistance exercise in women with osteoarthritis of the knee: a randomized controlled trial. Clinical Rehabilitation. 2015 Mar;29(3):234-43. doi: 10.1177/0269215514540920. PMID: WOS:000352000500004.

33. Singh S, Pattnaik M, Mohanty P, et al. Effectiveness of hip abductor strengthening on health status, strength, endurance and six minute walk test in participants with medial compartment symptomatic knee osteoarthritis. J Back Musculoskelet Rehabil. 2016;29(1):65-75. doi: 10.3233/bmr-150599. PMID: 26406217.

34. Fitzgerald GK, Piva SR, Gil AB, et al. Agility and perturbation training techniques in exercise therapy for reducing pain and improving function in people with knee osteoarthritis: a randomized clinical trial. Phys Ther. 2011 Apr;91(4):452-69. doi: 10.2522/ptj.20100188. PMID: 21330451.

35. Henriksen M, Klokker L, Graven-Nielsen T, et al. Association of exercise therapy and reduction of pain sensitivity in patients with knee osteoarthritis: a randomized controlled trial. Arthritis Care Res (Hoboken). 2014 Dec;66(12):1836-43. doi: 10.1002/acr.22375. PMID: 24905427.

36. Ju SB, Park GD, Kim SS. Effects of proprioceptive circuit exercise on knee joint pain and muscle function in patients with knee osteoarthritis. J Phys Ther Sci. 2015 Aug;27(8):2439-41. doi: 10.1589/jpts.27.2439. PMID: 26357422.

37. da Silva FS, de Melo FE, do Amaral MM, et al. Efficacy of simple integrated group rehabilitation program for patients with knee osteoarthritis: Single-blind randomized controlled trial. J Rehabil Res Dev. 2015;52(3):309-22. doi: 10.1682/jrrd.2014.08.0199. PMID: 26237073.

38. Barduzzi GO, Rocha Júnior PR, Souza Neto JC, et al. [Functional capacity of elderly with osteoarthritis who undergone to aquatic and land physical therapy]. Fisioterapia em Movimento; 2013. p. 349-60.

39. Segal NA, Glass NA, Teran-Yengle P, et al. Intensive Gait Training for Older Adults with Symptomatic Knee Osteoarthritis. Am J Phys Med Rehabil. 2015 Oct;94(10 Suppl

1):848-58. doi: 10.1097/phm.0000000000000264. PMID: 25768068.

40. Knoop J, Dekker J, van der Leeden M, et al. Knee joint stabilization therapy in patients with osteoarthritis of the knee: a randomized, controlled trial. Osteoarthritis Cartilage. 2013 Aug;21(8):1025-34. doi: 10.1016/j.joca.2013.05.012. PMID: 23721797.

41. Brosseau L, Wells GA, Kenny GP, et al. The implementation of a community-based aerobic walking program for mild to moderate knee osteoarthritis: a knowledge translation randomized controlled trial: part II: clinical outcomes. BMC Public Health. 2012;12:1073. doi: 10.1186/1471-2458-12-1073. PMID: 23234575.

42. Samut G, Dincer F, Ozdemir O. The effect of isokinetic and aerobic exercises on serum interleukin-6 and tumor necrosis factor alpha levels, pain, and functional activity in patients with knee osteoarthritis. Mod Rheumatol. 2015 May 27:1-6. doi: 10.3109/14397595.2015.1038425. PMID: 25849853.

43. Salacinski AJ, Krohn K, Lewis SF, et al. The effects of group cycling on gait and pain-related disability in individuals with mild-to-moderate knee osteoarthritis: a randomized controlled trial. J Orthop Sports Phys Ther. 2012 Dec;42(12):985-95. doi: 10.2519/jospt.2012.3813. PMID: 22951360.

44. Schlenk EA, Lias JL, Sereika SM, et al. Improving physical activity and function in overweight and obese older adults with osteoarthritis of the knee: a feasibility study. Rehabil Nurs. 2011 Jan-Feb;36(1):32-42. PMID: 21290963.

45. Koli J, Multanen J, Kujala UM, et al. CLINICAL SCIENCES Effects of Exercise on Patellar Cartilage in Women with Mild Knee Osteoarthritis. Medicine & Science in Sports & Exercise. 2015 September 2015;47(9) PMID: 109090545.

46. Christensen R, Henriksen M, Leeds AR, et al. Effect of weight maintenance on symptoms of knee osteoarthritis in obese patients: a twelve-month randomized controlled trial. Arthritis Care Res (Hoboken). 2015 May;67(5):640-50. doi: 10.1002/acr.22504. PMID: 25370359.

47. Lim JY, Tchai E, Jang SN. Effectiveness of aquatic exercise for obese patients with knee osteoarthritis: a randomized controlled trial. Pm r. 2010 Aug;2(8):723-31; quiz 93. doi: 10.1016/j.pmrj.2010.04.004. PMID: 20709301.

48. Rosedale R, Rastogi R, May S, et al. Efficacy of exercise intervention as determined by the McKenzie System of Mechanical Diagnosis and Therapy for knee osteoarthritis: a randomized controlled trial. J Orthop Sports Phys Ther. 2014 Mar;44(3):173-81, a1-6. doi: 10.2519/jospt.2014.4791. PMID: 24450370.

49. Abbott JH, Chapple CM, Fitzgerald GK, et al. The Incremental Effects of Manual Therapy or Booster Sessions in Addition to Exercise Therapy for Knee Osteoarthritis: A Randomized Clinical Trial. J Orthop Sports Phys Ther. 2015 Sep 28:1-9. doi: 10.2519/jospt.2015.6015. PMID: 26416334.

50. de Rooij M, van der Leeden M, Cheung J, et al. Efficacy of tailored exercise therapy on physical functioning in patients with knee osteoarthritis and comorbidity: A randomized controlled trial. Arthritis Care Res (Hoboken). 2016 Aug 26doi: 10.1002/acr.23013. PMID: 27563831.

51. Fitzgerald GK, Fritz JM, Childs JD, et al. Exercise, manual therapy, and use of booster sessions in physical therapy for knee osteoarthritis: a multi-center, factorial randomized clinical trial. Osteoarthritis Cartilage. 2016 Aug;24(8):1340-9. doi: 10.1016/j.joca.2016.03.001. PMID: 26973326.

52. Tsai PF, Chang JY, Beck C, et al. A pilot cluster-randomized trial of a 20-week Tai Chi program in elders with cognitive impairment and osteoarthritic knee: effects on pain and other health outcomes. J Pain Symptom Manage. 2013 Apr;45(4):660-9.

doi: 10.1016/j.jpainsymman.2012.04.009. PMID: 23017610.

53. Chenchen W, Schmid CH, Iversen MD, et al. Comparative Effectiveness of Tai Chi Versus Physical Therapy for Knee Osteoarthritis: A Randomized Trial. Annals of Internal Medicine. 2016;165(2):77-86. doi: 10.7326/M15-2143. PMID: 116901077. Language: English. Entry Date: In Process. Revision Date: 20160817. Publication Type: journal article. Journal Subset: Biomedical.

54. Cheung C, Wyman JF, Resnick B, et al. Yoga for managing knee osteoarthritis in older women: a pilot randomized controlled trial. BMC Complement Altern Med. 2014;14:160. doi: 10.1186/1472-6882-14-160. PMID: 24886638.

55. Cheawthamai K, Vongsirinavarat M, Hiengkaew V, et al. A comparison of home-based exercise programs with and without self-manual therapy in individuals with knee osteoarthritis in community. J Med Assoc Thai. 2014 Jul;97 Suppl 7:S95-100. PMID: 25141536.

56. Cortes Godoy V, Gallego Izquierdo T, Lazaro Navas I, et al. Effectiveness of massage therapy as co-adjuvant treatment to exercise in osteoarthritis of the knee: a randomized control trial. J Back Musculoskelet Rehabil. 2014;27(4):521-9. doi: 10.3233/bmr-140476. PMID: 24867903.

57. Azlin MNN, Lyn KS. Effects of Passive Joint Mobilization on Patients with Knee Osteoarthritis. Sains Malaysiana. 2011 Dec;40(12):1461-5. PMID: WOS:000299019800017.

58. Atkins DV, Eichler DA. The effects of self-massage on osteoarthritis of the knee: a randomized, controlled trial. Int J Ther Massage Bodywork. 2013;6(1):4-14. PMID: 23482239.

59. Dwyer L, Parkin-Smith GF, Brantingham JW, et al. Manual and manipulative therapy in addition to rehabilitation for osteoarthritis of the knee: assessor-blind randomized pilot trial. J Manipulative Physiol Ther. 2015 Jan;38(1):1-21.e2. doi: 10.1016/j.jmpt.2014.10.002. PMID: 25455832.

60. Perlman AI, Ali A, Njike VY, et al. Massage therapy for osteoarthritis of the knee: a randomized dose-finding trial. PLoS One. 2012;7(2):e30248. doi: 10.1371/journal.pone.0030248. PMID: 22347369.

61. Zhang Y, Shen CL, Peck K, et al. Training Self-Administered Acupressure Exercise among Postmenopausal Women with Osteoarthritic Knee Pain: A Feasibility Study and Lessons Learned. Evid Based Complement Alternat Med. 2012;2012:570431. doi: 10.1155/2012/570431. PMID: 23193423.

62. Fioravanti A, Giannitti C, Bellisai B, et al. Efficacy of balneotherapy on pain, function and quality of life in patients with osteoarthritis of the knee. Int J Biometeorol. 2012 Jul;56(4):583-90. doi: 10.1007/s00484-011-0447-0. PMID: 21573819.

63. Kulisch A, Benko A, Bergmann A, et al. Evaluation of the effect of Lake Heviz thermal mineral water in patients with osteoarthritis of the knee: a randomized, controlled, single-blind, follow-up study. Eur J Phys Rehabil Med. 2014 Aug;50(4):373-81. PMID: 24594851.

64. Mahboob N, Sousan K, Shirzad A, et al. The efficacy of a topical gel prepared using Lake Urmia mud in patients with knee osteoarthritis. J Altern Complement Med. 2009 Nov;15(11):1239-42. doi: 10.1089/acm.2009.0304. PMID: 19922256.

65. Fioravanti A, Bacaro G, Giannitti C, et al. One-year follow-up of mud-bath therapy in patients with bilateral knee osteoarthritis: a randomized, single-blind controlled trial. Int J Biometeorol. 2015 Sep;59(9):1333-43. doi: 10.1007/s00484-014-0943-0. PMID: 25516113.

66. Yildirim N, Filiz Ulusoy M, Bodur H. The effect of heat application on pain, stiffness, physical function and quality of life in

patients with knee osteoarthritis. J Clin Nurs. 2010 Apr;19(7-8):1113-20. doi: 10.1111/j.1365-2702.2009.03070.x. PMID: 20492056.

67. Hsieh RL, Lo MT, Lee WC, et al. Therapeutic effects of short-term monochromatic infrared energy therapy on patients with knee osteoarthritis: a double-blind, randomized, placebo-controlled study. J Orthop Sports Phys Ther. 2012 Nov;42(11):947-56. doi: 10.2519/jospt.2012.3881. PMID: 22960644.

68. Cakir S, Hepguler S, Ozturk C, et al. Efficacy of therapeutic ultrasound for the management of knee osteoarthritis: a randomized, controlled, and double-blind study. Am J Phys Med Rehabil. 2014 May;93(5):405-12. doi: 10.1097/phm.0000000000000033. PMID: 24322433.

69. Carlos KP, Belli BS, Alfredo PP. Effect of pulsed ultrasound and continuous ultrasound linked to exercise in patients with knee osteoarthritis: pilot study. Fisioterapia e Pesquisa; 2012. p. 275-81.

70. Kapci Yildiz S, Unlu Ozkan F, Aktas I, et al. The effectiveness of ultrasound treatment for the management of knee osteoarthritis: a randomized, placebo-controlled, double-blind study. Turkish Journal of Medical Sciences. 2015;45(6):1187-91. doi: 10.3906/sag-1408-81. PMID: WOS:000365510300001.

71. Gschiel B, Kager H, Pipam W, et al. [Analgesic efficacy of TENS therapy in patients with gonarthrosis. A prospective, randomised, placebo-controlled, double-blind study]. Schmerz. 2010 Sep;24(5):494-500. doi: 10.1007/s00482-010-0957-4. PMID: 20706740.

72. Atamaz FC, Durmaz B, Baydar M, et al. Comparison of the efficacy of transcutaneous electrical nerve stimulation, interferential currents, and shortwave diathermy in knee osteoarthritis: a double-blind, randomized, controlled, multicenter study. Arch Phys Med Rehabil. 2012 May;93(5):748-56. doi: 10.1016/j.apmr.2011.11.037. PMID: 22459699.

73. Palmer S, Domaille M, Cramp F, et al. Transcutaneous electrical nerve stimulation as an adjunct to education and exercise for knee osteoarthritis: a randomized controlled trial. Arthritis Care Res (Hoboken). 2014 Mar;66(3):387-94. doi: 10.1002/acr.22147. PMID: 23983090.

74. Inal EE, Eroglu P, Yucel SH, et al. Which is the Appropriate Frequency of TENS in Managing Knee Osteoarthritis: High or Low Frequency? Journal of Clinical and Analytical Medicine. 2016 May;7(3):339-44. doi: 10.4328/JCAM.3387. PMID: WOS:000376566800013.

75. Laufer Y, Shtraker H, Elboim Gabyzon M. The effects of exercise and neuromuscular electrical stimulation in subjects with knee osteoarthritis: a 3-month follow-up study. Clin Interv Aging. 2014;9:1153-61. doi: 10.2147/cia.s64104. PMID: 25083133.

76. Mizusaki Imoto A, Peccin S, Gomes da Silva KN, et al. Effects of neuromuscular electrical stimulation combined with exercises versus an exercise program on the pain and the function in patients with knee osteoarthritis: a randomized controlled trial. Biomed Res Int. 2013;2013:272018. doi: 10.1155/2013/272018. PMID: 24151589.

77. Imoto AM, Peccin MS, Teixeira LE, et al. Is neuromuscular electrical stimulation effective for improving pain, function and activities of daily living of knee osteoarthritis patients? A randomized clinical trial. Sao Paulo Med J. 2013;131(2):80-7. PMID: 23657509.

78. Elboim-Gabyzon M, Rozen N, Laufer Y. Does neuromuscular electrical stimulation enhance the effectiveness of an exercise programme in subjects with knee osteoarthritis? A randomized controlled trial. Clin Rehabil. 2013 Mar;27(3):246-57. doi: 10.1177/0269215512456388. PMID: 22952305.

79. Nelson FR, Zvirbulis R, Pilla AA. Non-invasive electromagnetic field therapy

produces rapid and substantial pain reduction in early knee osteoarthritis: a randomized double-blind pilot study. Rheumatology International. 2013 Aug;33(8):2169-73. PMID: WOS:000322120400037.

80. Dundar U, Asik G, Ulasli AM, et al. Assessment of pulsed electromagnetic field therapy with Serum YKL-40 and ultrasonography in patients with knee osteoarthritis. Int J Rheum Dis. 2015 May 8doi: 10.1111/1756-185x.12565. PMID: 25955771.

81. Bagnato GL, Miceli G, Marino N, et al. Pulsed electromagnetic fields in knee osteoarthritis: a double blind, placebo-controlled, randomized clinical trial. Rheumatology (Oxford). 2016 Apr;55(4):755-62. doi: 10.1093/rheumatology/kev426. PMID: 26705327.

82. Avelar NC, Simao AP, Tossige-Gomes R, et al. The effect of adding whole-body vibration to squat training on the functional performance and self-report of disease status in elderly patients with knee osteoarthritis: a randomized, controlled clinical study. J Altern Complement Med. 2011 Dec;17(12):1149-55. doi: 10.1089/acm.2010.0782. PMID: 22087576.

83. Rabini A, De Sire A, Marzetti E, et al. Effects of focal muscle vibration on physical functioning in patients with knee osteoarthritis: a randomized controlled trial. Eur J Phys Rehabil Med. 2015 Oct;51(5):513-20. PMID: 25990196.

84. Wang P, Yang L, Liu C, et al. Effects of Whole Body Vibration Exercise associated with Quadriceps Resistance Exercise on functioning and quality of life in patients with knee osteoarthritis: A randomized controlled trial. Clin Rehabil. 2015 Oct 1doi: 10.1177/0269215515607970. PMID: 26427960.

85. Wang P, Yang L, Li H, et al. Effects of whole-body vibration training with quadriceps strengthening exercise on functioning and gait parameters in patients with medial compartment knee osteoarthritis: a randomised controlled preliminary study. Physiotherapy. 2015 May 15doi: 10.1016/j.physio.2015.03.3720. PMID: 26111989.

86. Simao AP, Avelar NC, Tossige-Gomes R, et al. Functional performance and inflammatory cytokines after squat exercises and whole-body vibration in elderly individuals with knee osteoarthritis. Arch Phys Med Rehabil. 2012 Oct;93(10):1692-700. doi: 10.1016/j.apmr.2012.04.017. PMID: 22546535.

87. Park YG, Kwon BS, Park JW, et al. Therapeutic effect of whole body vibration on chronic knee osteoarthritis. Ann Rehabil Med. 2013 Aug;37(4):505-15. doi: 10.5535/arm.2013.37.4.505. PMID: 24020031.

88. Bokaeian HR, Bakhtiary AH, Mirmohammadkhani M, et al. The effect of adding whole body vibration training to strengthening training in the treatment of knee osteoarthritis: A randomized clinical trial. J Bodyw Mov Ther. 2016 Apr;20(2):334-40. doi: 10.1016/j.jbmt.2015.08.005. PMID: 27210851.

89. Callaghan MJ, Parkes MJ. A randomised trial of a brace for patellofemoral osteoarthritis targeting knee pain and bone marrow lesions. 2015 Jun;74(6):1164-70. doi: 10.1136/annrheumdis-2014-206376. PMID: 25596158.

90. Cherian JJ, Bhave A, Kapadia BH, et al. Strength and Functional Improvement Using Pneumatic Brace with Extension Assist for End-Stage Knee Osteoarthritis: A Prospective, Randomized trial. Journal of Arthroplasty. 2015 1;30(5):747-53. PMID: 2014984002 FULL TEXT LINK http://dx.doi.org/10.1016/j.arth.2014.11.036.

91. Sattari S, Ashraf AR. Comparison the effect of 3 point valgus stress knee support and lateral wedge insoles in medial compartment knee osteoarthritis. Iran Red Crescent Med J. 2011 Sep;13(9):624-8. PMID: 22737536.

92. Rodrigues PT, Ferreira AF, Pereira RM, et al. Effectiveness of medial-wedge insole treatment for valgus knee osteoarthritis. Arthritis and rheumatism; 2008. p. 603-8.

93. Koca B, Oz B, Olmez N, et al. Effect of lateral-wedge shoe insoles on pain and function in patients with knee osteoarthritis. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi. 2009 December;55(4):158-62. PMID: 2010074832.

94. Hatef MR, Mirfeizi Z, Sahebari M, et al. Superiority of laterally elevated wedged insoles to neutrally wedged insoles in medial knee osteoarthritis symptom relief. Int J Rheum Dis. 2014 Jan;17(1):84-8. doi: 10.1111/1756-185x.12036. PMID: 24472270.

95. Campos GC, Rezende MU, Pasqualin T, et al. Lateral wedge insole for knee osteoarthritis: randomized clinical trial. Sao Paulo Med J. 2015 Feb;133(1):13-9. doi: 10.1590/1516-3180.2013.6750002. PMID: 25626851.

96. Wallace DA. Efficacy of lateral heel wedge orthotics for the treatment of patients with knee osteoarthritis. Oregon State University. 2006 PMID: 109847445.

97. Toda Y, Tsukimura N. A 2-year follow-up of a study to compare the efficacy of lateral wedged insoles with subtalar strapping and in-shoe lateral wedged insoles in patients with varus deformity osteoarthritis of the knee. Osteoarthritis and Cartilage. 2006 March;14(3):231-7. PMID: 2006107628 MEDLINE PMID 16271485 (http://www.ncbi.nlm.nih.gov/pubmed/16271485) FULL TEXT LINK http://dx.doi.org/10.1016/j.joca.2005.09.006.

98. Bennell KL, Bowles KA, Payne C, et al. Lateral wedge insoles for medial knee osteoarthritis: 12 Month randomised controlled trial. Bmj. 2011;342(7808) PMID: 2011293830 MEDLINE PMID 21593096 (http://www.ncbi.nlm.nih.gov/pubmed/21593096) FULL TEXT LINK http://dx.doi.org/10.1136/bmj.d2912.

99. Goldenstein-Schainberg C, Fuller R, Matias A, et al. Effectiveness of long-term use of minimalist footwear on pain and function in knee osteoarthritis. Osteoporosis international; 2013. p. S139.

100. Trombini-Souza F, Matias A, Yokota M, et al. Beneficial effect of long-term use of a low-cost minimalist footwear on joint load, clinical, and functional aspects of elderly women with knee osteoarthritis. Arthritis and rheumatism; 2013. p. S918.

101. Trombini-Souza F, Matias AB, Yokota M, et al. Long-term use of minimal footwear on pain, self-reported function, analgesic intake, and joint loading in elderly women with knee osteoarthritis: A randomized controlled trial. Clin Biomech (Bristol, Avon). 2015 Aug 14doi: 10.1016/j.clinbiomech.2015.08.004. PMID: 26307181.

102. Erhart JC, Mundermann A, Elspas B, et al. Changes in Knee Adduction Moment, Pain, and Functionality with a Variable-Stiffness Walking Shoe after 6 Months. Journal of Orthopaedic Research. 2010 Jul;28(7):873-9. PMID: WOS:000278654500006.

103. Jones A, Silva PG, Silva AC, et al. Impact of cane use on pain, function, general health and energy expenditure during gait in patients with knee osteoarthritis: a randomised controlled trial. Ann Rheum Dis. 2012 Feb;71(2):172-9. doi: 10.1136/ard.2010.140178. PMID: 22128081.

104. Ghroubi S, Elleuch H, Kaffel N, et al. [Contribution of exercise and diet in the management of knee osteoarthritis in the obese]. Annales de réadaptation et de médecine physique : revue scientifique de la Société française de rééducation fonctionnelle de réadaptation et de médecine physique; 2008. p. 663-70.

105. Miller GD, Nicklas BJ, Davis C, et al. Intensive weight loss program improves physical function in older obese adults with knee osteoarthritis. Obesity (Silver Spring). 2006 Jul;14(7):1219-30. doi: 10.1038/oby.2006.139. PMID: 16899803.

106. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. Jama. 2013 Sep 25;310(12):1263-73. doi: 10.1001/jama.2013.277669. PMID: 24065013.

107. Bliddal H, Leeds AR, Stigsgaard L, et al. Weight loss as treatment for knee osteoarthritis symptoms in obese patients: 1-year results from a randomised controlled trial. Ann Rheum Dis. 2011 Oct;70(10):1798-803. doi: 10.1136/ard.2010.142018. PMID: 21821622.

108. Somers TJ, Blumenthal JA, Guilak F, et al. Pain coping skills training and lifestyle behavioral weight management in patients with knee osteoarthritis: a randomized controlled study. Pain. 2012 Jun;153(6):1199-209. doi: 10.1016/j.pain.2012.02.023. PMID: 22503223.

109. Bartels EM, Christensen R, Christensen P, et al. Effect of a 16 weeks weight loss program on osteoarthritis biomarkers in obese patients with knee osteoarthritis: a prospective cohort study. Osteoarthritis Cartilage. 2014 Nov;22(11):1817-25. doi: 10.1016/j.joca.2014.07.027. PMID: 25106676.

110. Atukorala I, Makovey J, Lawler L, et al. Is there a dose response relationship between weight loss and symptom improvement in persons with knee osteoarthritis? Arthritis Care & Research. 2016;[Epub ahead of print]doi: DOI 10.1002/acr.22805.

111. Makovey J, Lawler L, Bennell KL, et al. Dose response relationship between weight loss and improvement in quality of life in persons with symptomatic knee osteoarthritis. Osteoarthritis and Cartilage. 2015 April;23 SUPPL. 2:A386.

112. Claes BEA, Leung HWC, Matters K, et al. Interim analysis: An interdisciplinary team approach in facilitating weight reduction and improving function for people with knee or hip osteoarthritis. The Osteoarthritis Chronic Care Program at Royal North Shore Hospital. Nutrition & Dietetics. 2015 Sep;72(3):232-9. PMID: WOS:000362590300006.

113. Richette P, Poitou C, Garnero P, et al. Benefits of massive weight loss on symptoms, systemic inflammation and cartilage turnover in obese patients with knee osteoarthritis. Ann Rheum Dis. 2011 Jan;70(1):139-44. doi: 10.1136/ard.2010.134015. PMID: 20980288.

114. Stefanik J, Felson DT, Niu J, et al. The Relation of Massive Weight Loss to Changes in Knee Pain and Sensitization [abstract]. 2015 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2015;67 (suppl 10):3251.

115. Coleman S, Briffa NK, Carroll G, et al. A randomised controlled trial of a self-management education program for osteoarthritis of the knee delivered by health care professionals. Arthritis Res Ther. 2012;14(1):R21. doi: 10.1186/ar3703. PMID: 22284848.

116. Regnaux JP, Lefevre-Colau MM, Trinquart L, et al. High-intensity versus low-intensity physical activity or exercise in people with hip or knee osteoarthritis. Cochrane Database Syst Rev. 2015;10:Cd010203. doi: 10.1002/14651858.CD010203.pub2. PMID: 26513223.

117. Tubach F, Ravaud P, Martin-Mola E, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: Results from a prospective multinational study. Arthritis Care Res (Hoboken). 2012 Nov;64(11):1699-707. doi: 10.1002/acr.21747. PMID: 22674853.

118. McAlindon TE, Driban JB, Henrotin Y, et al. OARSI Clinical Trials Recommendations: Design, conduct, and

reporting of clinical trials for knee osteoarthritis. Osteoarthritis Cartilage. 2015 May;23(5):747-60. doi: 10.1016/j.joca.2015.03.005. PMID: 25952346.

119. Cho JJ, Kim TW, Park YM, et al. Tissuegene-C (InvossaTM) in patients with osteoarthritis: A phase II trials. Cytotherapy. 2015 June;17(6 SUPPL. 1):S84.

120. Cho J, Kim T, Park Y, et al. Tissuegene-C (Invossa™) in patients with osteoarthritis: A phase II trials. Osteoarthritis and Cartilage. 2015 April;23 SUPPL. 2:A170.

121. Lee B, Cho J, Kim T, et al. Tissuegene-C (TG-C), TGF-β1 transduced chondrocyte, improved clinical scores in patients with osteoarthritis: A phase 2B study. Molecular Therapy. 2014 June;22 SUPPL. 1:S292-S3.

122. Ha CW, Cho JJ, Elmallah RK, et al. A Multicenter, Single-Blind, Phase IIa Clinical Trial to Evaluate the Efficacy and Safety of a Cell-Mediated Gene Therapy in Degenerative Knee Arthritis Patients. Hum Gene Ther Clin Dev. 2015 Jun;26(2):125-30. doi: 10.1089/humc.2014.145. PMID: 25760423.

123. Messier SP, Callahan LF, Golightly YM, et al. OARSI Clinical Trials Recommendations: Design and conduct of clinical trials of lifestyle diet and exercise interventions for osteoarthritis. Osteoarthritis and Cartilage. 2015 May;23(5):787-97. PMID: WOS:000353821200011.

124. Fitzgerald GK, Hinman RS, Zeni J, Jr., et al. OARSI Clinical Trials Recommendations: Design and conduct of clinical trials of rehabilitation interventions for osteoarthritis. Osteoarthritis Cartilage. 2015 May;23(5):803-14. doi: 10.1016/j.joca.2015.03.013. PMID: 25952351.

125. Anwer S, Alghadir A, Brismee JM. Effect of Home Exercise Program in Patients With Knee Osteoarthritis: A Systematic Review and Meta-analysis. J Geriatr Phys Ther. 2016 Jan-Mar;39(1):38-48. doi: 10.1519/jpt.0000000000000045. PMID: 25695471.

126. Hochberg MC, Clegg DO. Potential effects of chondroitin sulfate on joint swelling: a GAIT report. Osteoarthritis Cartilage. 2008;16 Suppl 3:S22-4. doi: 10.1016/j.joca.2008.06.024. PMID: 18768335.

127. Kan L, Zhang J, Yang Y, et al. The Effects of Yoga on Pain, Mobility, and Quality of Life in Patients with Knee Osteoarthritis: A Systematic Review. Evid Based Complement Alternat Med. 2016;2016:6016532. doi: 10.1155/2016/6016532. PMID: 27777597.

128. Duivenvoorden T, Brouwer Reinoud W, van Raaij Tom M, et al. Braces and orthoses for treating osteoarthritis of the knee. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2015.

Introduction

Background and Objectives

Osteoarthritis (OA) of the knee is a condition characterized by the progressive destruction of the cartilage that lines the knee joints, the subchondral bone surfaces, and synovium; accompanied by pain, immobility, muscle weakness, and reduction in function and the ability to complete activities of daily living (ADLs). In 2005, the estimated prevalence of OA in any joint among adults in the United States (the number of individuals who had ever been told by a doctor that they had the condition) was approximately 27 million cases.[1] Prevalence rates vary by the joint involved and the method of ascertainment (clinical vs. radiographic): symptomatically, the knee is the most frequently affected joint.[2] The prevalence of OA of the knee is increasing rapidly because of shifting population demographics: The primary risk factors for OA of the knee are aging, obesity, prior injury, repetitive use,[3] and female gender. The U.S. Centers for Disease Control have estimated that the prevalence of symptomatic knee OA may reach 50 percent by the age of 85.[4] From 2002 to 2012, the number of individuals in the US with a total knee replacement (TKR) doubled from some 2 million to approximately 4 million.[5] The increase in obesity has translated not only into an increase in incidence of OA of the knee but also into a younger age of onset and need for treatment; as a result, by the time individuals with OA of the knee reach the age of Medicare eligibility, the length of time they have had the condition has grown, their cases are more advanced,[6] and the risk that surgery will be needed has increased. Thus, the aging of the Baby Boomer population, along with the increased incidence and prevalence of obesity have increased the risk for this condition, all representing an increasing strain on Medicare resources.

Etiology

Two types of OA of the knee are recognized: the more prevalent primary OA of the knee is the result of the progressive destruction of joint cartilage over time, whereas secondary OA of the knee can be caused by trauma, inactivity, overweight, or a disease process such as rheumatoid arthritis. No evidence suggests that the two types are treated differently or respond differently to treatments.[7] Therefore, the remainder of this report treats them as one entity.

Diagnosis

The clinical diagnosis of OA of the knee is typically based on presentation, including insidious onset of weight-bearing knee pain that is exacerbated by use of the joint and relieved by rest, and that tends to worsen over the course of the day. Radiographic evidence of OA may precede symptomatic OA but may not correlate with symptom severity. Radiologic severity can be estimated and expressed using the Kellgren and Lawrence (K-L) criteria. However, a number of versions of the criteria exist. In addition, at less severe grades, correlation with symptoms is poor,[8] whereas at more sever grades, agreement tends to be higher. The primary impact of the different versions of the criteria may be the challenge that they create in trying to assess, compare, and pool the findings of research studies.[8] Some longitudinal studies have even used different criteria at different time points within the same study. Because of the variation in scores for radiographic finding under various versions of the criteria (especially for individuals with less-advanced disease), stratification of findings by some other objective functional baseline criteria is important.

Some evidence suggests that among individuals with knee pain, MRI demonstrates physical signs of osteoarthritic changes in the knee before they are visible radiographically.[9] However, the sensitivity and specificity of MRI in diagnosis and monitoring of progression have not yet been definitively demonstrated and are not yet used in clinical practice.

Treatment Strategies

The goals of treatment for OA of the knee include relief of pain and inflammation, reduction of stiffness and improvement or preservation of range of motion, and improvement in or maintenance of mobility, function (including ADLs), and health-related quality of life (HRQoL).

Treatment options for OA of the knee include those in the following list. Information on the U. S. Food and Drug Administration status, indications, and warnings for the treatments included in this review (indicated by boldface and italics in this list) is included in Appendix G.

- Analgesics (oral, intra-articular, or topical) and anti-inflammatory agents (nonsteroidal anti-inflammatory agents [NSAIDs], intraarticular corticosteroids);
- Dietary supplements (including ***glucosamine with or without chondroitin*** and herbal mixtures), variously proposed to control pain and possibly serve as disease-modifying agents;
- Ayurvedic preparations, Traditional Chinese Medicine preparations, and acupuncture, all aimed at analgesia;
- ***Physical treatments*** (including strength or aerobic exercise, physical therapy, stretching, heat, aqua-therapy, whole-body vibration, electrical stimulation therapies (neuromuscular electrical stimulation [NMES] and transcutaneous electrical nerve stimulation [TENS]), massage, and chiropractic manipulation), proposed to strengthen muscles that support the affected joints and to increase range of motion;
- ***Education in pain coping strategies, self-management***, and activity modification;
- ***Orthoses (knee braces, shoe inserts, custom shoes, and canes***, intended to slow progression by shifting the weight from the affected joint area or other adaptive equipment to improve patients' environments;
- ***Weight loss*** to decrease the stress on the joint;
- Intraarticular viscosupplementation, which involves local injections of the natural joint lubricant, hyaluronic acid (HA),
- Biologic agents (antinerve growth factor antibodies or antitumor necrosis factor antibodies, which are used to treat rheumatoid arthritis, and may have some benefit for OA)
- Injections of ***platelet-rich plasma (PRP), plasma products, stem cells, and cartilage tissue***, also aimed at reversing or slowing the progression of the disease.[10]
- Surgical procedures, including arthroscopy with lavage and/or debridement, and partial or total arthroplasty (knee replacement), which may be recommended for advanced cases if patients fail to obtain satisfactory relief from pain and improved function from the aforementioned treatments.

Numerous recent evidence-based treatment guidelines have been issued, including the 2012 American College of Rheumatology Guidelines[10] and the 2013 American Academy of Orthopedic Surgeons guidelines for the treatment of OA of the knee. These guidelines are not in total agreement about the recommended treatments: For example the 2012 American College of

Rheumatology (ACR) Guidelines conditionally recommend hyaluronic acid (HA), while the American Academy of Orthopaedic Surgeons (AAOS) guidelines recommend against its use to treat patients with symptomatic conditions.[11]

Scope and Key Questions

Scope of the Review

Systematic reviews have been conducted on many of the interventions used to treat OA of the knee, including four reviews by Agency for Healthcare Research and Quality Evidence-based Practice Centers since 2007.[7, 12-14] Uncertainty continues to surround the use of all treatments intended as disease-modifying agents (including HA and glucosamine and chondroitin), acupuncture, physical therapy, exercise, braces and orthotics, and arthroscopic lavage, as well as the comparative efficacy and safety of oral, topical, and intraarticular analgesics and anti-inflammatories.

This review aimed to update a systematic review that was conducted in 2007.[7] That review assessed the efficacy and safety of HA, glucosamine and/or chondroitin, and arthroscopic surgery (the title of the original review, "Treatment of Primary and Secondary OA of the Knee: an Update Review," was changed to "Treatment of OA of the Knee"). Prior to preparing this review, we conducted an updating surveillance assessment that comprised an environmental scan and consultation with a Technical Expert Panel (TEP) to assess the currency of the conclusions of the 2007 review.[15] A document that summarized the findings of this bifurcated process was posted for public review.[16] The treatment interventions selected for inclusion in this review reflect a combination of the findings of the environmental scan, the TEP for the Surveillance process, the public comments, and the TEP for the current review.

The TEP for the surveillance process uniformly advised us that the conclusions of the 2007 report for intraarticular HA, oral glucosamine chondroitin, and arthroscopic surgery remained current and did not need updating. Instead, they recommended reviewing cell-based therapies, physical interventions, SNRIs (serotonin–norepinephrine reuptake inhibitor), topical agents, weight loss, and acupuncture.

The environmental scan supported the TEP's suggestion that the topics of intra-articular HA and arthroscopic surgery did not need updating. However, we identified several large recent trials on glucosamine-chondroitin that prompted us to want to update the review on this topic. In addition, we elected to review the topics of cell-based therapies and weight loss and to update a 2012 systematic review on physical interventions.[13] Topics recommended by the TEP but not included in this report will be re-assessed for the need to update (or to conduct a new review) in a later surveillance period.

The included topics (interventions) are listed in the Population, Intervention, Comparison, Outcome, Timing, Study Design, and Setting (PICOTs) outline (Table 1).

Table 1. PICOTs for the review

Category	Inclusions	Exclusions	Key Question(s)
Participant Population	Adults (age 18 or over) with a diagnosis of OA of the knee, as defined by the American Academy of Orthopaedic Surgeons (AAOS, 2013), ACR clinical classification criteria,[17] or	Studies of individuals under age 18; those with OA caused by a congenital condition; and those with OA concomitant with a meniscal or anterior cruciate ligament tear will be excluded because these participants have	KQ 1 and 2

Category	Inclusions	Exclusions	Key Question(s)
	Kellgren-Lawrence stage	conditions that differ importantly from the vast majority of OA patients	
	Subpopulations of interest include those defined by: sex, disease subtype (e.g., patellofemoral, or medial tibiofemoral), disease severity (stage/pain or functional status), body mass index, fitness/activity level, prior treatment, concurrent treatment(s), comorbidities	Studies that include those who have had knee replacement surgery on the affected limb or for whom outcomes will be measured after knee replacement surgery or who have concomitant joint disease such as rheumatoid arthritis or gout will be excluded because these conditions or procedures will confound assessment of the outcomes of interventions	KQ 1 and 2
Interventions	Glucosamine and/or chondroitin	RCTs with <50 participants	KQ 1 and 2
	Cell-based therapies: • Platelet-rich plasma • Intraarticular or arthroscopic administration of mesenchymal stem-cells or chondrocytes or tissue	Phase I or II trials will not be included for efficacy, as the interventions are generally not FDA-approved for use	
	Strength/resistance training	RCTs with<50 participants; Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Agility exercise	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Aerobic exercise	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Physical therapy/general exercise programs	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Manual therapy	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Balneotherapy (including mud therapy, as the proposed mechanisms overlap)	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Heat/infrared/ultrasound	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Neuromuscular electrical stimulation (NMES)	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Transcutaneous electrical nerve stimulation (TENS)	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Whole-body vibration	RCTs where effects of intervention could not be isolated	
	Braces/orthotics/shoes/cane	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Weight loss: both RCTs and single-arm trials included	None	
	Self-management programs where participants were taught techniques to control pain and	None	

Category	Inclusions	Exclusions	Key Question(s)
	improve function, if they included physical interventions		
Comparators	Glucosamine/chondroitin: placebo-controlled or head-to-head noninferiority only	Studies that use the untreated knee, participants themselves, or a treatment of unestablished efficacy as a control	KQ 1 and 2
	Cell-based therapies: placebo- or sham-controlled only	Studies that use the untreated knee, participants themselves, or a treatment of unestablished efficacy as a control	
	Physical treatments and/or weight loss: placebo-controlled, usual care-controlled, or wait list-controlled only except for weight loss	Studies that use the untreated knee, participants themselves, or a treatment of unestablished efficacy as a control	
	NMES/TENS: sham stimulation without current Wait list Treatment as usual	Studies that use the untreated knee, participants themselves, or a treatment of unestablished efficacy as a control	
Outcomes	Short-term clinical outcomes: Pain (e.g., WOMAC, VAS, KOOS,) Joint stiffness (WOMAC) Function (WOMAC, Lequesne, others) Total WOMAC OARSI physical outcomes (e.g., timed up-and-go, 6-minute walk test,) Patient Reported Outcome Measurement System (PROMIS®) and Osteoarthritis-Computer Adaptive Test (OA-CAT) Inflammation or effusion Medication use	Studies that report only nonclinical outcomes (e.g., muscle strength measures, joint space, interleukin levels)	KQ 1
	Long-term clinical outcomes: Instrumental activities of daily living (IADLs) Quality of life (e.g., SF-36, EuroQuol EQ-5D, Arthritis Self-Efficacy scale, global assessment, patient satisfaction) Surgery (i.e., rate of undergoing knee replacement) Any of the short-term clinical outcomes		
	Adverse events	Studies that fail to report adverse event data separately by study arm will not be included in the adverse event analysis	KQ 2
Timing of followup	≥4 weeks (1 month) from baseline	Studies with maximum follow-up 4 weeks or less	KQ 1 and 2
Study design	RCTs (single arm and prospective cohort studies included for weight loss)	Open trials (except weight loss)	KQ 1 and 2
		Studies that fail to report outcomes for knee alone	KQ 1 and 2
	Large prospective studies		KQ 2

Category	Inclusions	Exclusions	Key Question(s)
Settings	Any setting		KQ 1 and 2

Abbreviations: AAOS=American Academy of Orthopaedic Surgeons; ACR=American College of Rheumatology; IADL=Independent Activities of Daily Living; KOOS=Knee injury and Osteoarthritis Score; KQ=Key Question; NMES=Neuromuscular electrical stimulation; OA=Osteoarthritis; Osteoarthritis Computer Adapted Test=OA-CAT; OARSI=Osteoarthritis Research Society International; PICOTS=Population, Intervention, Comparator, Outcomes, Timing, Study design/Setting(s); RCT=randomized controlled trial; TENS=trans-cutaneous electrical nerve stimulation; VAS=Visual Analog Scale; WOMAC=Western Ontario and McMaster Universities Arthritis Index

Key Questions

Based on the findings of the environmental scan, TEP assessments, and public comments, the Key Questions from the 2007 report were revised as follows.

Key Question 1a: What is the clinical effectiveness of cell-based therapies, oral glucosamine and/or chondroitin, physical treatment interventions, weight loss, or home-based and self-management therapies in patients with OA of the knee, compared with appropriate placebo/sham controls or compared with other active interventions?

Key Question 1b: How do the outcomes of each intervention differ by the following population and study characteristics: sex, disease subtype (lateral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

Key Question 2a: What harms are associated with each intervention in patients with OA of the knee?

Key Question 2b: How do the harms associated with each intervention differ by the following population or study characteristics: sex, disease subtype (lateral tibiofemoral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

Analytic Framework

The review was guided by the analytic framework shown in Figure 1.

Figure 1. Analytic framework for osteoarthritis of the knee

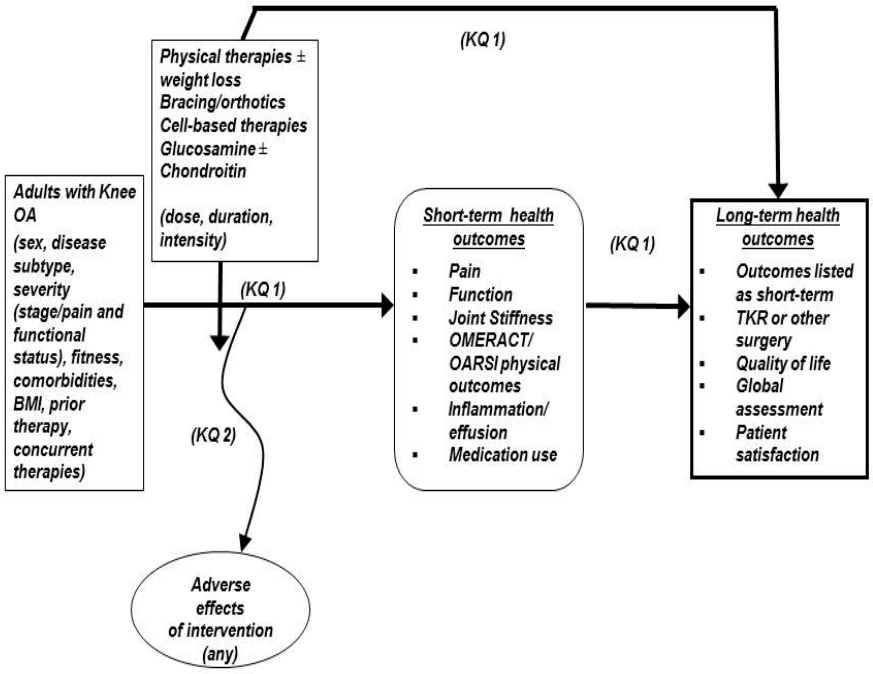


Figure notes: BMI = Body Mass Index; KQ = Key Question; OA = Osteoarthritis; OARSI = Osteoarthritis Research Society International; OMERACT = Outcome Measures in Rheumatology; TKR = Total Knee Replacement.

Organization of This Report

The remainder of this report presents the methods used to conduct the literature searches, data abstraction, and analysis for this review; the results of the literature searches, organized by KQ and intervention; the conclusions; and a discussion of the findings within the context of what is already known, the limitations of the review and the literature, and suggestions for future research.

Methods

The methods used to conduct the systematic review portion of this continuous update are based on the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[15]

Criteria for Inclusion/Exclusion of Studies in the Review

Included studies are limited to those that fit the inclusion and exclusion criteria listed in Table 1.

Studies in any clinical setting were included as long as they satisfied all other inclusion/exclusion criteria. The results of the report are intended for primary care and acute care settings, and therefore primary and acute settings are preferred. For studies of efficacy and effectiveness, we endeavored to include only randomized controlled trials. However, in the absence of relevant randomized controlled trials, observational studies were included. Observational studies were also included if they reported rare adverse events. Case reports were excluded.

Existing systematic reviews were also considered for inclusion both as sources of original data (reference mining) and for their conclusions, following the methods proposed by Whitlock and colleagues.[18]

Searching for the Evidence

The inclusion/exclusion criteria by target population, interventions, outcomes, comparators, setting, and study duration are shown in Table 1. Study design and several additional criteria pertaining to the PICOTs (the Population, Intervention, Comparison, Outcome, Timing, Study Design, and Setting that describe the scope of the review) are discussed here and below.

English language studies and those with an English–language abstract were included, if resources were available for translation. We excluded publications with both nonEnglish abstracts and text, because of limited resources. Studies that test interventions that were not available in the US were also excluded. Studies that assessed the effects of glucosamine and/or chondroitin were included only if they enrolled 50 participants or more per arm because of the number of very large clinical trials. Conference proceedings and letters that reported unique data and that reported sufficient information to enable assessment of risk of bias were included.

With the exception of weight loss trials, we limited included studies for assessment of efficacy to randomized controlled trials. We included single-arm trials and prospective cohort studies for weight loss. We included prospective observational studies that reported on adverse events associated with use of the interventions of interest for the treatment of osteoarthritis (OA) of the knee.

Studies without participant and assessor blinding were excluded for dietary supplements and cell-based therapies, based on the findings of prior reviews that the results of such studies can bias the results. However, for studies of physical therapies for which it is difficult to design a placebo control and implement participant blinding, we included studies in which the intervention group was not blinded to their assignment. Studies that compared an intervention of interest only to an intervention with no demonstrated evidence of efficacy (or unclear evidence of efficacy, such as intraarticular hyaluronic acid) were excluded. Also, studies that combined interventions were included only if the control “intervention” allowed assessment of the specific intervention of interest (e.g., neuromuscular electrical stimulation [NMES] plus strength training

versus strength training). Studies were not excluded simply because of low study quality (risk of bias).

The searches commenced with the year 2006, one year prior to the latest search dates of the original review we are updating.[7] However, because we are also updating topics covered in an EPC review conducted in 2012,[19] we did not re-review studies included in (or actively excluded from) that review unless the study included a treatment group or outcome of interest that the original review did not evaluate. Similarly, when we identified recent systematic reviews on other included topics (e.g., braces and orthotics) that match our review in Key Questions, outcomes of interest, and exclusion/inclusion criteria, we weighed the feasibility of updating those reviews with any newer original studies rather than simply using those reviews as sources of references and conducting entirely new reviews (see Data Synthesis/Analysis). However, ultimately, we did not include any prior systematic reviews as sources of evidence. The full search methodology is in Appendix A. An update search was conducted in September 2016.

Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

Based on the methods used for the original report and recent reviews on similar topics, we searched the following databases for peer reviewed literature (dates discussed above): PubMed, EMBASE, the Cochrane Collection, Web of Science, and the Physiotherapy Evidence Database (PEDRO). Based on pilot searches of these databases, we did not include PEDRO search results.

The Web of Science and ClinicalTrials.gov was searched for grey literature and as-yet unpublished peer-reviewed articles, respectively; and the abstracts from the past year of professional practice society annual meetings (e.g., American College of Rheumatology, American Academy of Orthopaedic Surgery) were hand searched by members of the team with the appropriate clinical expertise. In addition, relevant stakeholders, including manufacturers of over-the-counter and prescription medications and medical devices used to treat OA of the knee were contacted by the Evidence-based Practice Center (EPC) Program's Scientific Resource Center for scientific information packets that contain any unpublished information on the efficacy and/or safety of their products when used specifically to treat OA of the knee; no information was obtained from manufacturers. A notice was also placed in the Federal Register requesting any relevant information on the use of dietary supplements containing glucosamine or chondroitin to treat OA of the knee.

Titles identified by literature searches were screened by pairs of experienced literature reviewers using prespecified criteria, without reconciliation of decisions. Abstracts of those titles selected for inclusion by one or both reviewers were dually screened using prespecified criteria, with disagreements reconciled by the project leaders, if necessary. Full text articles or other documents were obtained for included abstracts. DistillerSR™ software was used for screening, abstraction, reconciliation, and tracking. A 10-percent sample of titles for which no abstract could be identified in the databases was obtained and reviewed in full-text to determine whether we should obtain the full-text publications for all titles of interest that lack an abstract. Such publications are typically commentaries, editorials, and letters to journal editors without original data. Based on the sample screen, which identified no studies that met inclusion criteria, we determined that these publications would not be screened further.

Any references that were suggested by members of the TEP, peer reviewers, or public reviewers were obtained and underwent the same screening and abstraction process. Reference

lists from recent systematic reviews on the topics of interest were also screened for relevant articles that had not appeared in the search output.

We conducted an update search during peer review and included the relevant studies from the update search into the final report.

Data Abstraction and Data Management

Study-level details were dually abstracted by the reviewers, using abstraction forms designed and piloted by the group (with at least two design iterations and some 10 to 25 articles piloted per iteration, as suggested by the issues that arose during piloting). Disagreements were reconciled between reviewers with mediation by the project leaders if needed. NonEnglish articles were obtained and abstracted only if a native or knowledgeable speaker was identified. Outcome data were abstracted by experienced reviewers and an experienced biostatistical analyst and audited by an experienced reviewer. Risk of bias was assessed by one reviewer and audited by a second reviewer with extensive systematic review experience. If primary outcome data appeared to be lacking for a particular study, we did not contact study authors.

Studies that reported outcomes in multiple publications were noted, the publications mapped, and the records linked in Distiller to ensure consistency and avoid duplication of descriptions of study conditions. In such cases, risk of bias (RoB) was assessed at the publication (rather than at the study) level.

The following study-level details were abstracted: mean participant age (by study or study arm), sex, mean body mass index, OA diagnoses (stage, pain levels, functional status and activity level), relevant comorbidities, concurrent or prior treatments; numbers of participants enrolled and numbers who completed; inclusion/exclusion criteria; interventions and comparators, type and location of study site; number of sites; study and investigator funding; and potential conflicts of interest. Information collected as part of assessing risk of bias is described below.

Assessment of Methodological Risk of Bias of Individual Studies

For randomized controlled trials, we employed the Cochrane Risk of Bias Assessment tool to assess RoB of individual studies. We also incorporated a small number of items from the PEDro risk of bias assessment tool. A recent analysis finds that the tools produce different assessments of the same studies, with the Cochrane tool providing a more rigorous assessment.[20] Characteristics assessed included evidence of accepted methods for ensuring unbiased recruitment, randomization, and allocation concealment (selection bias); participant blinding (performance bias); assessor blinding (detection bias); description of prespecified outcomes (reporting bias); retention (attrition bias), and adherence, use of intention-to-treat analysis, and power calculation (other bias). For each of ten such factors, we assessed whether the factor contributed to a low, high, or unclear risk of bias. Based on the overall assessment, studies were rated as having a low, moderate, high, or unclear risk of bias.

We used the McHarms scale to assess the quality of adverse event assessment and reporting. Adverse events whose numbers were reported separately by treatment group were abstracted and categorized as being serious or nonserious.[21]

Data Synthesis/Analysis

Results of included studies are described by intervention type. Within each intervention type, studies are described by duration of followup and by outcome type (pain, function, and other).

Results of studies that compared different interventions head to head are described in the sections of the Results chapter that pertain to each of the interventions of interest.

Effect sizes and confidence intervals were calculated for each outcome based on differences at follow-up (baseline values were assumed to be statistically similar).

In the case of a continuous outcome, the primary measure collected was the follow-up mean and standard deviation. If the follow-up mean was not reported, then the mean change from baseline was collected. If the standard deviation or standard errors were not reported and could not be calculated from a confidence interval, then the interquartile range or range of the scale was used to estimate a standard error. For binary outcomes, we collected the number of people with the event of interest.

For continuous measures, standardized mean differences were calculated using Cohen's d. Risk ratios were calculated for binary outcomes.

Outcome data were stratified by length of time from baseline. Short-term outcomes were 4 to 12 weeks, medium-term outcomes were 12 to 26 weeks, and long-term outcomes were longer than 26 weeks. If a study reported outcomes at more than one short-, medium-, or long-term time period, we abstracted the longer one(s).

If three or more studies reported the same outcome measure for the same intervention during the same follow-up time period, we pooled the outcomes using the Hartung Knapp method for random effects meta-analysis.[22] Because some studies did not report the scales used for outcome measures and because it was not always possible to determine the scales from the data, we report pooled outcomes as standardized mean differences; we did not pool studies that used different tools to measure a similar outcome (e.g., the Visual Analog Scale [VAS] and the Western Ontario and McMaster Universities Arthritis Index [WOMAC] pain measures), as two tools used in the same study on the same participant population sometimes resulted in different outcomes. If a study reported outcomes for pain or function using multiple outcome measures, all outcomes were abstracted, but WOMAC outcomes were given preference in analyses. The findings of meta-analyses are reported quantitatively with forest plots. All studies for which results are included in the report are described qualitatively (narratively) by the type of intervention and the duration of followup. Descriptions of studies of similar interventions were grouped by outcome measures when feasible.

For pooled studies with significant outcomes, we assessed whether these outcomes met a prespecified minimum clinically important difference (MCID). If studies reported whether their outcomes met a prespecified MCID or improvement (MCII) or reported on the percent of participants who achieved a response, we noted that in the narrative descriptions.

Grading the Strength of Evidence (SoE) for Major Comparisons and Outcomes

We rated the strength of evidence (SoE) of each intervention-outcome-followup time based on the AHRQ Methods Guide. Domains include the following:

- Study limitations (study design, risk of bias [RoB],
- Overall methodological quality),
- Consistency of the direction of effect sizes across studies, or within a single study, if the study reported the same outcome using more than one assessment tool).
- Precision of the estimate (including number of studies), assessed in terms of the similarity in effect sizes, the average variance, and the numbers of studies

- Directness of the relationship between outcomes measured and the clinical outcomes of interest, and
- Magnitude of the effect size.

Based on these domains, we rated the SoE for each comparison of interest as high, moderate, low, or insufficient (if no or too few studies were identified that addressed the outcome):

- High strength of evidence: We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions
- Moderate strength of evidence: We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains
- Low strength of evidence: We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect
- Insufficient evidence: We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion

For outcomes for which no pooling was possible, we estimated a rating based on qualitative assessment of the individual studies that met the inclusion criteria. Overall study quality was assessed identically as for pooled studies (considering study design and average RoB). Factors that led to downgrading of SoE were lack of pooling, number of studies fewer than three, inconsistency across or within studies, imprecision (confidence intervals wider than approximately four times the effect size), and poor study quality. Directness was rated but was not a factor, as only studies with clinical outcomes were included. We rated applicability of participant populations and interventions separately, as described below.

Trial design was considered in grading SoE as it was a factor in considering study quality. For assessments of safety, we considered the consistency of the findings across trials in assigning a SoE grade.

Assessing Applicability

We considered applicability of participants and interventions separately from our assessment of directness for SoE. For assessing applicability of participant populations, studies that enrolled younger age populations (mean age less than 50), those with only early stage or mild disease, those enrolling participants with mean BMI less than 25, or those with a higher activity level at baseline were considered less applicable.

For assessing applicability of interventions, studies of interventions with very high adherence (especially physical activity) were considered somewhat less applicable than studies with lower adherence.

Follow-up times for studies of OA are nearly always too short for a chronic, progressive disease. Studies with shorter maximum follow-up times (less than 3 months) were considered to have lower applicability.

Peer Review and Public Commentary

A draft version of the draft report was posted for peer review and for public comments on September 12, 2016, and revised in response to comments. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

This section first describes the results of the literature searches, followed by descriptions of the studies that met inclusion criteria for each of the Key Questions (KQs) and the key points (conclusions).

Results of Literature Searches

Our searches identified 11,229 titles/abstracts. An additional search of grey literature and ClinicalTrials.gov resulted in 1,674 titles. Fifty-five references were suggested by experts or were meetings abstracts. This yielded 12,958 titles/abstracts that went out for dual screening, of which 9,433 titles were excluded. At abstract screening, 2,134 were excluded for the following reasons: not human (38), not a population of interest (87), not on osteoarthritis (OA) of the knee (215), not on treating or managing OA of the knee (192), not an intervention of interest (338), not an outcome of interest (247), study design (including editorials, letters, cross sectional study design, and protocols) (582), study was included in a previous Evidence-based Practice Center (EPC) review (135), maximum followup was less than 30 days (7), duplicate study (13), no abstract was indexed (245), or we were unable to retrieve the article (35).

We reviewed 647 full text articles, of which 541 were excluded for the following reasons: not human (6), not a population of interest (6), not on OA of the knee (28), not on treating or managing OA of the knee (6), not an intervention of interest (95), intervention (glucosamine) with a sample size of less than 50 (32), not an outcome of interest (28), study design (including editorials, letters, cross sectional study design, and protocols) (85), study was included in a previous EPC review (3), maximum followup was less than 30 days (36), comparators not of interest (70), no usable data (80), multi-component interventions (27), duplicate study (39). A list of references by exclusion reason can be found in Appendix B.

The Federal Register posting did not yield any additional materials to review for possible inclusion.

We include 107 new articles in our report of which 57 reported adverse events (AEs). Our literature flow diagram (Figure 2) displays our screening results. Appendix D contains our data abstraction tools that were used for abstracting the data of the 107 included studies. Appendix E shows strength of evidence, and Appendix F contains the quality assessment of each of the included studies.

Figure 2. Literature flow diagram

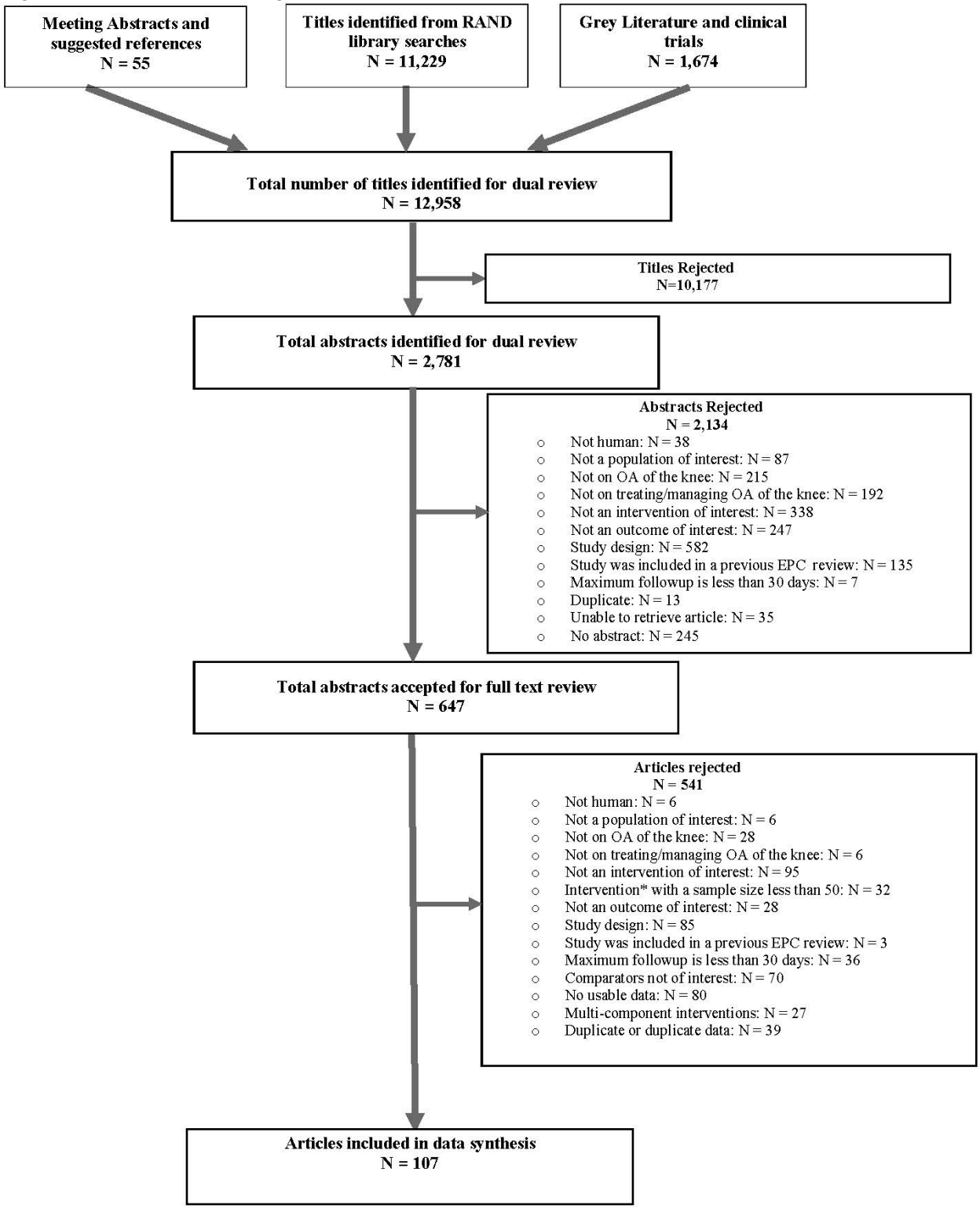


Figure notes: *Only glucosamine intervention with a sample size less than 50 participants were excluded; EPC=Evidence-based Practice Center; OA=osteoarthritis

Key Question 1a: What is the clinical effectiveness of cell-based therapies, oral glucosamine and/or chondroitin, physical treatment interventions, weight loss, or home-based and self-management therapies in patients with OA of the knee, compared with appropriate placebo/sham controls or compared with other active interventions?

Key Question 1b: How do the outcomes of each intervention differ by the following population and study characteristics: sex, disease subtype (lateral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

Description of Included Studies

Cell-Based Therapies

Cell-based therapies that were considered for treatment of OA of the knee included intra-articular injection of platelet-rich plasma (PRP) as well as introduction of stem cells. We did not identify any studies of stem cell treatments that met the inclusion criteria.

Key Points

- Among the cell-based therapies, only PRP was assessed in RCTs that met inclusion criteria for this review.
- A low strength of evidence based on four RCTs supports a beneficial effect of PRP on medium-term pain and quality of life.
- A low strength of evidence based on three RCTs supports a beneficial effect of PRP on medium-term quality of life.
- Evidence was insufficient to draw conclusions regarding the effects of PRP on medium-term function.
- Evidence was insufficient to draw conclusions regarding outcomes at shorter or longer times.

Findings

Platelet-Rich Plasma

Studies of PRP were included if they compared PRP to sham injections or to use of analgesics but not to injections of other potential therapeutic agents of unclear efficacy. We identified 5 RCTs that compared the use of autologous PRP to that of a sham control or analgesic.[23-27] The longest followup time was 6 months from baseline for all studies.

Short-term effects on pain. Three studies reported on short-term effects of PRP treatment on pain.[23, 26, 27]

A 2013 double-blind RCT conducted in India by Patel and coworkers randomized 78 patients into three treatment groups: a group that received one injection, a group that received two injections at baseline and at 3 weeks, and a control group, which received saline injections (RoB

moderate).[23] WOMAC pain scores at 6 weeks' followup were significantly decreased from baseline and from that of the control group in both active treatment groups (MD -5.22 for one injection, MD -5.10 two injections, at 6 weeks). No significant difference in pain scores or in mean duration of benefit (17 days) was seen between those receiving one injection and those receiving two injections. Response was positively associated with disease severity but not associated with age, sex, or BMI.

A 2014 RCT conducted in Mexico by Acosta-Olivo randomized 42 patients to receive two injections of PRP or instructions to take paracetamol 3 times daily for 30 days; each group also received a 6-month supervised physical rehabilitation program (RoB unclear).[26] At 4 months, KOOS pain scores were 51.2(15.4) and 42.2(14.7) for the PRP and control groups, and showed a nonsignificant between-group difference (MD –9.00, 95% CI –18.11, 0.11).

A 2016 RCT conducted in Mexico by Simental-Mendia and colleagues randomized 65 patients with grade 1 or 2 OA to receive three injections of leukocyte-poor PRP, biweekly, over 6 weeks, or to take acetaminophen (500 mg) 3 times daily for 6 weeks (RoB low).[27] At the end of the 6 weeks and at 12 weeks, VAS pain scores showed significantly greater improvement in the PRP group than in the control group (MD–2.20, 95% CI –3.25, –1.15).

Short-term effects on function. Patel[23] also assessed the effects of PRP on function and stiffness. At 6 weeks' followup, WOMAC function scores were significantly decreased from those of the control group in both active treatment groups (single injection: MD -15.56, dual injections: -16.24).

Short-term effects on other outcomes. Patel[23] also assessed the effects of PRP on WOMAC total scores. At 6 weeks follow-up, the MD was -21.42 for a single injection and -21.82 for dual injections.

At 12 weeks, Simental-Mendia[27] also reported a significant improvement in WOMAC total scores compared with analgesic (MD –13.4, 95% CI –20.00, –6.71) and on the physical domain of the SF-12 (MD –7.60, 95% CI –11.76, –3.48).

Medium-term effects on pain. Five RCTs assessed the effects of PRP injections at 6 months followup.[23-27]

Patel[23] reported increases in VAS and WOMAC pain scores in both the single- and double-injection groups compared with the earlier follow-up time, although scores remained significantly lower than control and baseline scores (MD -5.87 for one injection, MD -4.69 for two injections). VAS Pain was significantly decreased in both treatment groups compared with the control (single injection MD -2.45, 95% CI -2.92, -1.98; dual injections MD -2.07, 95% CI -2.59, -1.55).

A 2015 double-blind RCT conducted in Turkey by Görmeli and coworkers randomized 136 consecutive patients to receive a single injection of PRP, three injections of PRP, or a single saline injection (a fourth group received hyaluronic acid; results for this group will not be reported here) (RoB Low).[24] EuroQol VAS pain scores at 6 months' followup showed significant between-group differences for one injection (MD-14.00, 95% CI -11.56, -16.44) and three injections (MD-23.40, 95% CI -19.66, -27.14) of PRP compared with the control; three injections had significantly greater effects than a single injection ($p<0.001$). Treatment response was affected by severity of OA: patients with early (K-L grade I-III) OA achieved significantly greater pain control with three injections than with one injection ($p<0.005$), whereas among patients with advanced (K-L grade IV) OA three injections provided the same improvement as one injection.

A 2014 RCT conducted in Iran by Rayegani randomized 65 patients to receive two injections of PRP 4 weeks apart or no treatment.[25] Both groups were enrolled in an exercise protocol and prescribed acetaminophen as needed (RoB High). At 6 months' follow-up, the PRP group showed nonsignificantly greater improvement in WOMAC pain scores than did the control group (MD -0.96, 95% CI -2.88, 0.96).

At 6 months' followup, the Acosta-Olivo study reported that KOOS pain scores for the PRP group were significantly improved compared with the paracetamol group (MD −6.90, 95% CI−18.29, 4.49, p=0.0008) and a slight but insignificant decrease from the 4-month score.[26]

At 6 months, Simental-Mendia[27] reported no significant improvement in VAS pain scores compared with analgesic.

Medium-term effects on function. Patel[23] assessed the effects of PRP on function and stiffness. At 6 months' followup, WOMAC function scores were significantly decreased from that of the control group in both active treatment groups (MD -19.38 for single injection; -17.06 for dual injections).

The 2014 RCT by Rayegani showed no significant between-group difference in WOMAC function scores at 6 months.[25]

Medium-term effects on other outcomes. In the Patel study, WOMAC total scores in both treatment groups at 6 months' followup were also significantly decreased from those of the control group (MD -25.91 for single injection; MD -22.61 for dual injections).[24]

At 6 months followup, the study by Rayegani[25] showed a significant improvement in the SF-36 physical domain for the PRP-treated group compared with the control group (MD −1.00, variance not reported).

The 2015 Görmeli RCT reported significant between-group differences in quality of life in favor of PRP, as assessed with the EuroQuol (MD -14.00 95% CI -16.44, -11.56 for one injection; MD -23.40, 95% CI -27.14, -19.66 for three injections).[24]

At 6 months followup, the study by Simental-Mendia showed a sustained significant improvement in WOMAC total scores in the PRP-treated group compared with the analgesic group (MD –12.3, 95% CI –19.59, -5.01) and in the SF-12 physical domain (MD -9.90, 95% CI –14.67, –5.73) .[27]

Long-term effects. No studies reported on long-term effects of PRP.

Other Cell-Based Therapies

No studies were identified on other cell-based therapies that met the inclusion criteria for the report.

Glucosamine With or Without Chondroitin or Chondroitin Alone

Key Points

- Glucosamine, chondroitin, and the combination of glucosamine plus chondroitin have shown somewhat inconsistent beneficial effects in large, multi-site placebo-controlled and head-to-head trials.
- Glucosamine + chondroitin: Three large, multi-site RCTs and one smaller RCT found low strength of evidence for a medium-term effect on pain and function but moderate strength of evidence for no long-term benefit on pain and function.
    - Two of three trials showed a medium-term benefit of glucosamine plus chondroitin on both pain and function (low strength of evidence).

    - A random effects pooled estimate for three studies showed no effect of long-term treatment on pain compared with control (pooled effect size -0.73, 95% CI −4.03; 2.57) (moderate strength of evidence).
    - A random effects pooled estimate for all three studies showed no effect of long-term treatment on function compared with control (pooled effect size -0.45, 95% CI −2.75; 1.84) (moderate strength of evidence).
- Glucosamine alone: No RCTs met inclusion criteria for short- or medium-term outcomes. Three RCTs that assessed effects of long-term glucosamine showed a moderate strength of evidence for no beneficial effects on pain and low strength of evidence for no benefit on function.
    - A random effects pooled estimate of three studies showed no effect of long-term glucosamine treatment compared with control on pain (n=1007; pooled effect size −0.05, 95% CI −0.22; 0.12; I^2 0%) (moderate strength of evidence)
    - Effects of long-term glucosamine on function showed no consistent benefit (low strength of evidence)
- Chondroitin alone: Three RCTs that assessed effects of chondroitin alone on pain and function showed inconsistent effects across time and outcomes.
    - Two large RCTs showed significant medium-term benefit of chondroitin alone for pain (low strength of evidence). Evidence was insufficient to assess medium-term effects on function.
    - Three large RCTs showed no long-term benefit of chondroitin alone on pain (moderate strength of evidence) or function (low strength of evidence).
- No studies were identified that compared glucosamine sulfate with glucosamine hydrochloride.
- No studies analyzed the time course of effects of glucosamine and/or chondroitin, but studies that examined effects at multiple time points showed that the maximum effects are achieved at 3 to 6 months.

Findings

Because of the existence of several large RCTs, we limited our assessment to studies that enrolled at least 50 participants per study arm. The studies identified for this report include a 2-year followup assessment of GAIT results.[28]

Glucosamine Plus Chondroitin

Five RCTs identified for this report assessed the effects of glucosamine plus (combined with) chondroitin.[28-32] No studies reported on short-term outcomes as primary outcomes, although one study reported the trajectory of effects over 6 months.

Medium-term effects on pain. Three studies assessed medium-term effects of glucosamine plus chondroitin on pain.[29, 30, 32]

The Multicentre Osteoarthritis interVEntion trial with SYSADOA (MOVES) study is a 2016 multicenter noninferiority RCT aimed at comparing the efficacy and safety of glucosamine hydrochloride and/or chondroitin sulfate with that of celecoxib among patients with severe baseline knee pain (RoB low).[29] Six hundred three participants were randomized to receive 400 mg chondroitin sulfate plus 500 mg glucosamine hydrochloride three times a day or 200 mg celecoxib for 6 months. The adjusted mean difference in WOMAC pain and the VAS with glucosamine hydrochloride + chondroitin sulfate showed no difference compared with celecoxib,

confirming equivalence, and the decrease in pain was considered clinically significant (RR 1.00, 95% CI 0.85, 1.17).

A 2014 open RCT conducted in India by Bellare and colleagues randomized 117 overweight adults with knee OA to a low calorie weight loss diet with glucosamine (1500 mg/d) and chondroitin sulfate (1200 mg/d) supplementation or diet alone (RoB unclear).[30] The chemical form of glucosamine was not specified, and the diet only group did not receive a placebo. At 6 months, weight loss was the same in both groups. The group that received glucosamine and chondroitin had significantly greater improvements in pain than the diet only group, as shown by decrease in WOMAC pain scores (MD -1.59, 95% CI -2.31, -0.87) for the glucosamine plus chondroitin group compared with the diet only group, $p<0.05$) and VAS scores (MD -2.08, 95% CI -2.40, -1.76).

A 2016 RCT conducted in Spain by Roman-Blas (Herrero-Beaumont and colleagues) randomized 164 patients with knee OA (KL grade II-III) to a daily dose of glucosamine (1500 mg/d) and chondroitin sulfate (1200 mg/d) or placebo for 6 months (RoB low).[32] The placebo provided better pain relief than did the glucosamine-chondroitin, as measured on the VAS and on WOMAC scales.

Medium-term effects on function. The MOVES,[29] the diet study[30] and the Roman-Blas study[32] also reported on the medium-term effects of glucosamine plus chondroitin on function.

The MOVES Trial found no differences at 6 months between treatment groups in the WOMAC function score, with a decrease of 45.5% in the glucosamine plus chondroitin group compared with a decrease of 46.4% in the celecoxib group ($p=0.53$). The reduction in function was considered clinically important (RR 1.02, 95% CI 0.86, 1.21).

The Bellare diet study[30] reported significant improvements in WOMAC function scores and Lequesne function scores in both treatment groups. The group that received glucosamine plus sulfate showed significantly greater improvements in both WOMAC (MD -3.86, 95% CI -6.16, -1.56) and Lequesne (MD -2.56, 95% CI -3.35, -1.77) function measures than did the diet only group.

The Roman-Blas study found no difference between glucosamine plus chondroitin and placebo in WOMAC function.[32]

Medium-term effects on other outcomes. The MOVES study reported no difference in WOMAC stiffness scores between glucosamine plus chondroitin and celecoxib groups, with a decrease of 46.9% in the combination group, compared with a decrease of 49.2% in the celecoxib group ($p=0.43$). The improvement in stiffness was considered clinically significant.[29]

The Bellare study reported improvements in WOMAC stiffness scores in both groups with the group that received glucosamine plus chondroitin reporting greater improvements than the diet-only group (5.29[1.12] to 2.60[0.56] vs. 4.94[1.08] to 3.00[0.82], $p<0.05$).[30]

The MOVES study reported an OMERACT OARSI response rate of 79%. Similarly, no differences were observed in patients' ($p=0.51$) and physicians' ($p=0.33$) global assessments of disease activity or response to therapy ($p=0.74$ and 0.70, respectively) or in the Euroquol-5D assessment of HRQoL (MD 0.00).[29]

Long-term effects on pain. Three trials that met inclusion criteria assessed long-term effects of glucosamine and chondroitin on pain.[28, 30, 31] Because one study did not report variation, no pooling was possible.

The GAIT trial, whose 6-month outcomes were reported in the original report, compared the effects of glucosamine sulfate + chondroitin to those of placebo and celecoxib on the decrease in WOMAC pain score from baseline and on the likelihood of experiencing a 20% improvement in

pain at 2 years compared with placebo and with celecoxib (RoB low).[28] No significant sustained decreases in pain were seen between glucosamine plus chondroitin and placebo (MD 1.04, 95% CI -21.44, 23.51) or celecoxib and placebo (-13.54 (95% CI -35.92, 8.84). The likelihood of achieving a 20% improvement in WOMAC pain scores also did not differ between glucosamine plus chondroitin and celecoxib compared with placebo (OR 0.83, 95% CI 0.51, 1.34 vs. 1.21, 95% CI 0.71, 2.07). All results were adjusted for baseline age, sex, BMI, and K-L grade.

The Bellare open RCT described above assessed the effects of glucosamine plus chondroitin on pain at 12 months. Weight loss was the same in both groups. The group that received glucosamine and chondroitin had significantly greater improvements in pain than the diet only group, as shown by decrease in WOMAC pain scores (MD -3.10, 95% CI -3.69, -2.51) and VAS scores (MD -1.70, 95% -1.99, -1.41).[30]

The Long term Evaluation of Glucosamine Sulfate (LEGS) study, a 2014 placebo-controlled RCT, randomized 605 participants to receive glucosamine sulfate (750 mg) or placebo and chondroitin sulfate (400mg) or placebo once daily for 24 months (RoB low).[31] The primary outcomes for this study were joint space width (JSW) narrowing and pain. At both 1 and 2 years, participants who received glucosamine plus chondroitin experienced decreases in VAS and WOMAC pain scores (adjusted or unadjusted) that did not differ from those in the placebo group.

A random effects pooled estimate for all three studies showed no effect of treatment compared with the control on long-term pain; study heterogeneity was very high (pooled effect size -0.73, 95% CI −4.03; 2.57; I^2 97%) (Figure 3).

Figure 3. Forest plot for long-term effects of glucosamine-chondroitin on WOMAC pain score

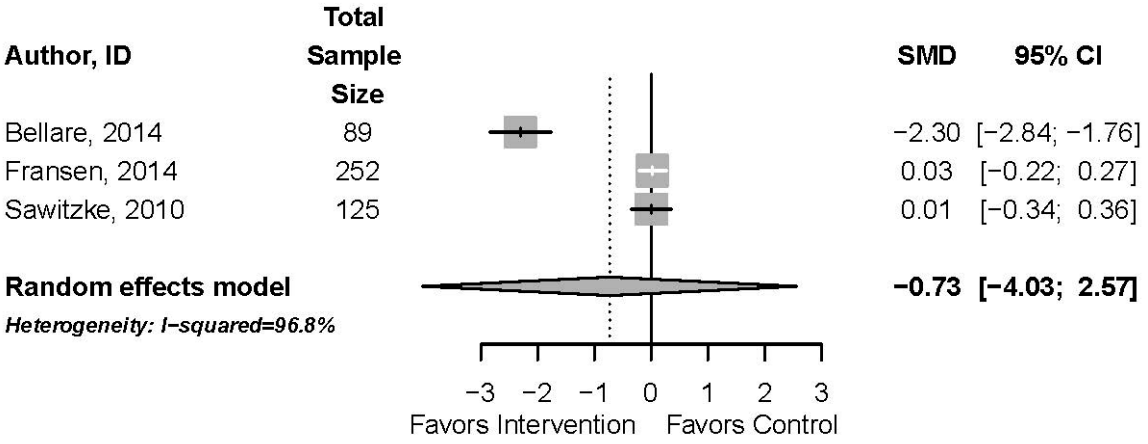


Figure notes: CI=confidence interval; EPC=Evidence-based Practice Center; SMD=standardized mean difference; OA=osteoarthritis; WOMAC=Western Ontario and McMaster Arthritis Index

Long-term effects on function. Three studies assessed the longer term effects of glucosamine plus chondroitin on function.[28, 30, 31] Because one study failed to report variation, no pooling was possible.

The GAIT trial found decreases (improvement) in WOMAC function scores at 2 years that did not differ from those of placebo or celecoxib.[28]

The Bellare open RCT described above assessed the effects of glucosamine plus chondroitin on function at 12 months. The group that received glucosamine and chondroitin had significantly

greater improvements in WOMAC function, (MD -7.90, 95% CI -10.06, -5.74) and Lequesne scores (0-24 points, MD -3.20, 95% CI -3.86, -2.54) than the diet only group.[30]

The LEGS study found at both 1 and 2 years that participants who received glucosamine plus chondroitin experienced decreases in WOMAC function scores (adjusted or unadjusted) that did not differ from those in the placebo group.

A random effects pooled estimate for all three studies showed no effect of treatment compared with the control on long-term function; study heterogeneity was very high (pooled effect size -0.45, 95% CI −2.75; 1.84; I^2 95%) (Figure 4).

Figure 4. Forest plot for long-term effects of glucosamine on WOMAC function score

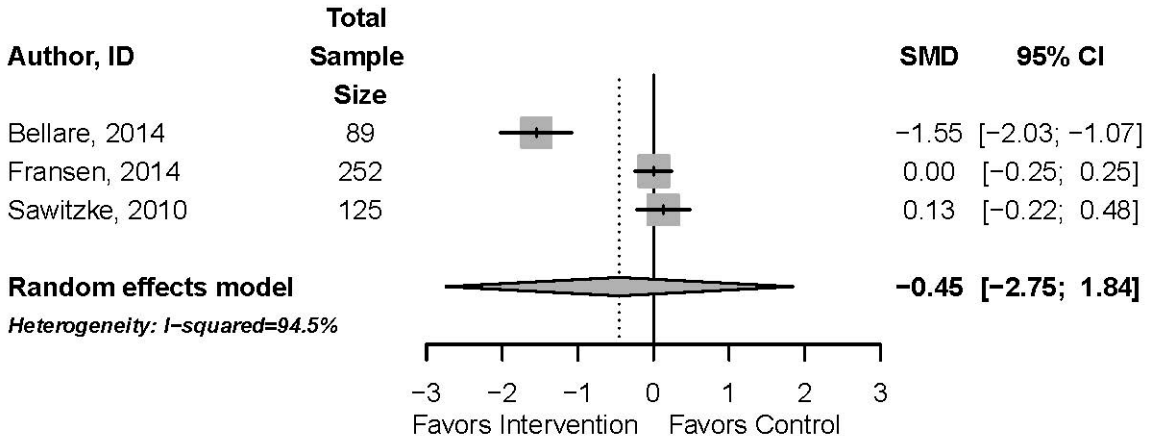


Figure notes: CI=confidence interval; SMD=standardized mean difference; WOMAC=Western Ontario and McMaster Arthritis Index

Long-term effects on other outcomes. Two studies assessed the longer term effects of glucosamine plus chondroitin on other outcomes.[30, 31]

The Bellare open RCT assessed effects of the combined supplement on the change in WOMAC stiffness scores at 12 months. The supplemented group experienced a significantly greater improvement in stiffness than the diet only group (mean change -3.95[1.15] vs. -2.80[1.01], $p<0.05$).[30]

The LEGS trial study found no difference between placebo and glucosamine-chondroitin in SF-12 physical domain scores at 12 months and 24 months.[31]

Glucosamine Alone

No studies that met inclusion criteria assessed the short- or medium-term effects of glucosamine alone. Two RCTs assessed the longer-term effects of glucosamine alone on pain and function among individuals with OA of the knee,[28, 31] and one post hoc analysis of two RCTs assessed the association between glucosamine sulfate supplementation and election to receive total knee replacement.[33]

Long-term effects on pain. The GAIT trial compared the effects of glucosamine sulfate alone to those of placebo and celecoxib on the decrease in WOMAC pain score from baseline and on the likelihood of experiencing a 20 percent improvement in pain at 2 years compared with placebo and with celecoxib.[28] Decreases from baseline did not differ between either treatment group and placebo. The likelihood of achieving a 20 percent improvement in WOMAC pain scores also did not differ between glucosamine and celecoxib compared with placebo (OR 1.16,

95% CI 0.65, 2.04 vs. 1.21, 95% CI 0.71, 2.07). All results were adjusted for baseline age, sex, BMI, and K-L grade.

The LEGS study found that at both 1 and 2 years, participants who received glucosamine sulfate alone experienced decreases in WOMAC pain scores (adjusted or unadjusted) that did not differ from those in the placebo group.[31]

A 2015 RCT conducted in Bulgaria by Stambolova Ivanova randomized 190 individuals with OA of the knee to receive glucosamine sulfate (1500 mg per day) or a placebo daily for 4 months per year for 3 years (RoB unclear; study reported as a conference proceeding abstract).[34] Both groups also participated in a physical activity program. At the end of the 3-year period, both groups demonstrated an increase in pain compared to baseline; however, the increase in pain, as measured with the VAS, was significantly lower for the group that received glucosamine (MD -4.60).

A random effects pooled estimate for all three studies showed no effect of glucosamine treatment compared with the control on long-term pain; study heterogeneity was very low (n=1007, pooled effect size -0.05, 95% CI −0.22; 0.12; I^2 0%) (Figure 5).

Figure 5. Forest plot for long-term effects of glucosamine on WOMAC pain score

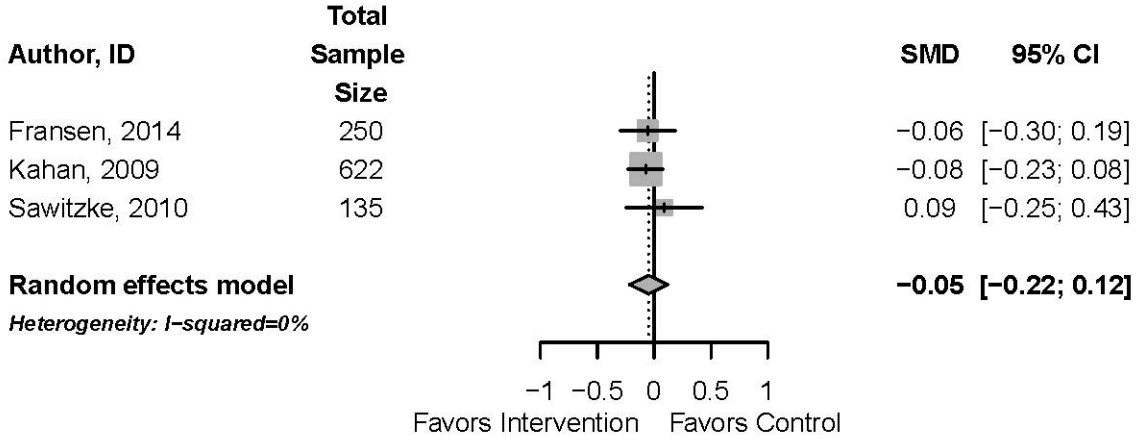


Figure notes: CI=confidence interval; SMD=standardized mean difference; WOMAC=Western Ontario and McMaster Arthritis Index

Long-term effects on function. The GAIT trial compared the effects of daily glucosamine sulfate alone to those of placebo and celecoxib on change in WOMAC function scores from baseline to 2 years compared with placebo and with celecoxib.[28] Changes from baseline did not differ between either treatment group and placebo: glucosamine 9.56 (95% CI -79.79, 98.91), celecoxib-15.82 (95% CI -102.31, 70.67). Results were adjusted for baseline age, sex, BMI, and K-L grade.

The LEGS study found that at both 1 and 2 years, participants who received glucosamine sulfate alone experienced decreases in WOMAC function scores (adjusted or unadjusted) that did not differ from those in the placebo group.[31]

The Stambolova Ivanova study compared function between the glucosamine sulfate and placebo-treated groups at 3 years using the Lequesne Index.[34] They reported that the placebo group experienced significantly worse function over the 3 years compared with that of the glucosamine treated group.

Long-term effects on other outcomes. Three studies assessed the longer-term effects of glucosamine alone on other outcomes.[28, 31, 33]

The GAIT trial compared the effects of glucosamine sulfate alone to those of placebo and celecoxib on the likelihood of achieving a 20 percent improvement in OMERACT-OARSI scores.[28] The risk did not differ between glucosamine compared with placebo or celecoxib compared with placebo (OR 1.16, 95% CI 0.74, 1.83 vs. 1.45, 95% CI 0.86, 2.42). All results were adjusted for baseline age, sex, BMI, and K-L grade.

The LEGS study found that at both 1 and 2 years, participants who received glucosamine sulfate alone experienced improvements in SF-12 physical component summary scores that did not differ from those in the placebo group.[31]

Bruyere and colleagues pooled the data from two 3-year placebo-controlled trials of glucosamine sulfate conducted in 2001 and 2002 to assess the association between use of the dietary supplement and long-term risk for TKR among some 414 adults with knee OA.[33, 35, 36] The primary outcome of the original trials had been joint space narrowing. Among 340 participants with 12 to 36 months of treatment, of whom 275 could be contacted, the average treatment follow up was 5 years. The risk for TKR was over twice as great among placebo treated participants as among the active (Risk of Bias low based on the two original RCTs).

Chondroitin Alone

Four trials assessed the effects of chondroitin alone compared with placebo.[28, 31, 37, 38]

Short-term effects on pain. One study that met inclusion criteria assessed short-term effects of chondroitin on pain. A 2013 multicenter placebo-controlled RCT by Zegels and colleagues compared the efficacy and safety of two dosing strategies for chondroitin sulfate among 353 participants over 3 months: a single 1200mg/d dose vs. 400mg/d, three times daily (RoB low).[37] The outcome for pain was the 100mm VAS scale. Per protocol analysis was used to test equivalence, and ITT analysis was used to test the comparison with placebo. At 1 and 2 months, no statistically significant differences were observed in VAS scores between the active treatment groups or between active treatments and placebo (p=0.43 and p=0.18, respectively).

Short-term effects on function. The dosing equivalence study by Zegels assessed the effects of chondroitin on function, as measured by the Lequesne Index, at 2 and 3 months of treatment.[37] At 2 months, no difference was observed between the two treatment groups: Both dosing forms showed significant benefit of the chondroitin sulfate compared with the placebo group (MD –1.50, 95% CI –2.62, –0.38 for one 1200mg dose and –1.50, 95% CI –2.59, –0.41) for three 400mg doses). At 3 months, the two active treatment groups showed identical mean differences in Lequesne scores (MD –1.90, 95% CI –3.11, –0.69 and –2.20, 95% CI –3.57, –1.03), which were significantly improved compared with the placebo group.[37]

Medium-term effects on pain. Two RCTs that met inclusion criteria for this report assessed medium-term effects of chondroitin on pain.[37, 38]

At 3 months post baseline, the dosing equivalence study by Zegels and colleagues found that both dosing options (1200mg once a day or 400 mg 3 times per day) had identical effects on VAS pain, significantly greater than the placebo effect (MD -7.70, 95% CI -14.43, -0.97 versus MD -8.30, 95% CI -15.20, -1.40).[37]

The Study on Osteoarthritis Progression Prevention (STOPP) was a two-year placebo-controlled multi-center RCT that assessed the efficacy and safety of chondroitin sulfate (800 mg/d for 24 months) on 622 participants with mild-to-moderate OA of the knee; the primary outcome was JSW (RoB low).[38] The (secondary) effects on pain were reported as the percent of responders. The percent of responders in the chondroitin group significantly exceeded that in the placebo group for 40mm decrease in VAS (RR 0.68, 95% CI 0.51, 0.91), 60mm decrease in VAS

(RR 0-.44, 95% CI 0.23, 0.85), and 40 percent reduction in WOMAC pain (RR 0.83, 95% CI 0.68, 1.02).

Medium-term effects on function. The STOPP Trial reported no difference between chondroitin sulfate and placebo in WOMAC function scores at 6 months (data not reported).[38]

At 3 months post baseline, the dosing equivalence study by Zegels and colleagues found that both dosing options (1200mg once a day or 400 mg 3 times per day) had similar effects on function, as measured by the Lequesne Index, both significantly greater than the placebo effect (MD -2.20, 95% CI -3.37, -1.03 versus MD -1.90, 95% CI -1.90, 95% CI -3.11, -0.69).[37]

Long-term effects on pain. Three RCTs reported on long-term WOMAC pain scores but no pooling was possible because one study failed to report variance.[28, 31, 38]

At 24 months, the STOPP Trial demonstrated sustained decreases in pain, as measured by the VAS and WOMAC; however, the difference between the chondroitin group and the placebo group was not significant.[38]

The 2-year follow up of the GAIT trial showed that chondroitin sulfate did not achieve a significant change in WOMAC pain (11.50, 95% CI -15.40, 38.40) or a clinically meaningful pain response (OR 0.69, 95% CI 0.40, 1.21) compared with placebo.[28]

At years 1 and 2, the LEGS Trial showed significant improvements from baseline for chondroitin in WOMAC pain scores, but no difference from that of the placebo group.[31]

Long-term effects on function. Two RCTs reported on long-term effects on function.[28, 31]

The 2-year follow up of the GAIT trial showed that chondroitin sulfate did not achieve a significant decrease in WOMAC function (OR 36.64, 95% CI -64.57, 37.86) compared with placebo.[28]

At years 1 and 2, the LEGS Trial showed significant improvements from baseline for chondroitin in WOMAC function scores, but no difference from that of the placebo group.[31]

Long-term effects on other outcomes. The STOPP Trial found no difference between groups in cumulative use of acetaminophen but a trend toward decreased use of NSAIDS in the chondroitin group compared with the placebo group at 2 years.[38]

Aerobic Exercise

Key Points

- Based on five trials, aerobic exercise alone shows no long-term benefit on function; evidence was insufficient to draw conclusions regarding its effects on short- or medium-term outcomes or on long-term pain for patients with knee OA.
    - Evidence was insufficient to draw conclusions about short-term effects of aerobic exercise on pain, function, and total WOMAC scores (one RCT).
    - Evidence was insufficient to draw conclusions about medium-term effects of aerobic exercise on pain, function, and total WOMAC scores (two RCTs).
    - Evidence was insufficient to draw conclusions on effects of long-term aerobic exercise on pain (2 RCTs)
    - Aerobic exercise showed no significant long-term effects on function, based on three RCTs (low evidence).

Findings

Aerobic exercise for the treatment of OA of the knee was limited to aerobic based exercise programs that did not include other exercise interventions, such as strength training. Studies were

included if they compared aerobic exercise to a control group, but not to other exercise programs. We identified five RCTs that compared an aerobic exercise program to a control group. [39-43] The longest follow-up time was 18 months.

Short-term effects on pain. One RCT reported on short-term effects of aerobic exercise on pain.[40]

A 2015 RCT conducted in Turkey by Samut and colleagues randomized 27 postmenopausal women and men 50 years of age or older with knee OA to a 3-session-per-week, 6-week progressive aerobic exercise (treadmill) intervention or to a usual care control group (Unclear RoB).[40] At 6 weeks, a significant between-group difference was observed in WOMAC pain scores, favoring the aerobic exercise intervention (MD −4.02, 95% CI −6.01, −2.03).

Short-term effects on function. At 6 weeks, the 2015 Samut RCT showed a significant between-group difference in WOMAC function scores (MD −15.35, 95% CI −24.02, −6.68).[40]

Short-term effects on other outcomes. At 6 weeks, the 2015 Samut RCT showed a significant between-group difference in WOMAC total scores (MD −18.58, 95% CI −29.65, −7.51), but not on the 6-minute walk test.[40]

Medium-term effects on pain. A 2012 RCT conducted in the US by Salacinski and colleagues randomized 37 adults with mild-to-moderate knee OA to a 12-week group cycling program or a wait list control group (Low RoB).[43]At the end of the 12-week period, a significant between-group difference was seen in WOMAC pain, favoring cycling (0-100 point scale, MD −14.9, 95% CI −27.0, −2.6).

Medium-term effects on function. Two studies reported on medium-term effects of aerobic exercise on function. As a feasibility study for the STAR intervention, a 2011 RCT conducted in the US randomized 26 overweight and obese adults, 50 years and over, to a 6-month walking program (moderate RoB).[42] The aim was to develop and test self-efficacy strategies to promote fitness walking in an individually delivered home-based program for overweight and obese older adults with knee OA. At the end of the 6-month program, no significant between-group differences were seen in WOMAC function or in performance on the 6-minute walk test.

At 12 weeks, the 2012 Salacinski RCT showed no significant between-group differences in WOMAC function scores.[43]

Medium-term effects on other outcomes. At 12 weeks, the 2012 Salacinski RCT showed a significant between-group difference in WOMAC stiffness scores (MD −10.8, 95% CI −21.3, −0.7) but not in WOMAC total scores or KOOS ADL scores.[43]

Long-term effects on pain. Three RCTs reported on the long-term effects of aerobic exercise on pain.[39, 41, 42]

A 2012 single-blind RCT conducted in Canada by Brosseau and colleagues randomized 222 patients into three treatment groups: a group that received a supervised aerobic walking program, behavioral intervention, and an educational brochure; a group that received a supervised walking program and an educational brochure; and a control group that received an educational brochure (RoB high).[39] The group receiving the behavioral intervention and walking program was excluded from this analysis. At 18-months follow-up, WOMAC pain scores were not significantly different between the control group and the aerobic walking program.

A 2015 RCT conducted in Finland by Koli and colleagues randomized 80 postmenopausal women with mild knee OA to a 3 times per week aerobics class or to an inactive control group for 12 months (moderate RoB).[41] At 12 months, no significant between-group differences were observed in KOOS pain.

Long-term effects on function. Three RCTs reported on the long-term effects of aerobic exercise on function.

The 2011 STAR feasibility test found no significant followup effects of the aerobic walking intervention at 12 months from baseline.[42]

Brosseau[39] examined the effects of their aerobic walking program on function as measured by WOMAC function scores. At 18 months follow-up, WOMAC function was not significantly different between the control group and the aerobic walking group.

The 2015 Koli RCT reported no significant effect of the aerobic exercise program on KOOS physical functioning at 12 months.[41]

Long-term effects on other outcomes. At 18 months follow-up, Brosseau [39] also reported no significant differences in total WOMAC scores, SF-36 functional domain scores, TUG scores, or 6-minute walk test distances between the control group and aerobic walking group.

Strength or Resistance Training

Key Points

- It is unclear whether strength and resistance training have a beneficial effect on patients with OA of the knee. Pooled analyses support a nonstatistically significant benefit, and individual study findings suggest possible benefit on pain and function and significant benefit on total WOMAC scores.
- Strength and resistance training had no statistically significant beneficial effect on short-term pain or function based on pooled analyses of 5 RCTs but a significant short-term beneficial effect on the composite WOMAC total score based on 3 RCTs (low strength of evidence).
- Strength and resistance training showed a nonsignificant medium-term beneficial effect on function in a pooled analysis of 3 RCTs (low strength of evidence).
- Evidence was insufficient to assess long-term effects of strength and resistance training.
- No studies assessed the effects of any factors such as sex, obesity, or disease severity on outcomes of strength and resistance training.

Findings

The current review defined an intervention as a strength- or resistance training intervention if the study authors explicitly called the intervention a strength or resistance training intervention or if the primary activity of the intervention (based on time spent on that activity) was aimed at improving strength or resistance. These studies generally included several sessions per week of therapist-led individual or group exercise (including a brief period of warm-up aerobic exercise prior to the strength training period and a cool down period following the strength training) with instructions to perform some exercises at home on the other days. The strength training protocols usually commenced with a level of resistance tailored to the individual that increased progressively with gain in strength. The details are described in the evidence table in Appendix C.

Short-term effects on pain. Five RCTs (reported in 6 publications) met our inclusion criteria for assessing short-term effects of strength training interventions on pain.[44-49]

A 2012 Brazilian RCT randomized 100 individuals with OA of the knee to an exercise femoral quadriceps strengthening (exercise) group or an educational group (RoB low).[47, 48] The exercise group attended an 8-week twice weekly physiotherapist-led class in which resistance

loads were individualized based on a ten-repetition maximum test. Both the exercise and the control groups received an educational manual about knee care (with no exercise instructions) and permission to use paracetamol. At 8 weeks, no significant between-group differences were seen in the exercise group compared with the instruction group in WOMAC pain scores[47] but a significant group difference was seen in NRS pain scores (MD -1.47, 95% CI -2.71, -0.23).[48]

A 2012 single-blind RCT conducted in Ireland by Bruce-Brand and colleagues randomized 41 adults with moderate to severe knee OA to a 6-week therapist-supervised home-based resistance training program, neuromuscular electrical stimulation, or a control group (education and physical therapy) (RoB moderate).[44] No improvement was observed in WOMAC pain scores at 8 weeks in the resistance training group compared with the control group. At baseline, the intervention groups differed in WOMAC pain scores, and the dropout rate was exceptionally high at followup.

A 2012 US RCT by Wortley randomized 31 older adults with OA of the knee to a 10-week resistance training program, a tai chi program, or a control group (RoB high).[45]At 10 weeks, WOMAC pain scores were not improved significantly compared to the control group.

A 2012 RCT conducted in the US by Rogers and coworkers randomized 44 adults age 50 and over to one of four 8-week home-based interventions: kinesthesia, balance, and agility (KBA) training alone, resistance training (RT) alone, a combination of KBA and RT, and a control group that received no intervention (RoB moderate).[46] At 4 and 8 weeks, WOMAC pain scores improved significantly for the strength training group compared with the control group (0-20 points, MD -3.75, 95% CI -6.39, -1.11).

A 2015 RCT conducted in Brazil by Jorge and coworkers randomized 60 postmenopausal women knee OA to a 12-week progressive knee and hip strength training program or to a wait-list control group (low RoB).[49] At 6 weeks, the resistance training group showed significant improvements in WOMAC (0-20 point scale, MD −3.40, 95% CI −5.10, −1.70) and VAS (0-10 point scale, MD −1.10, 95% CI −2.20, −0.17) pain scores compared with the control group.

Pooling the results for WOMAC pain for the five studies showed that resistance training had no significant effect on short-term pain; heterogeneity was moderately high (n=215; random effects estimate MD −0.55, 95% CI −1.46, 0.37; I^2 72%) (Figure 6).

Figure 6. Forest plot for short-term effects of strength training on WOMAC pain score

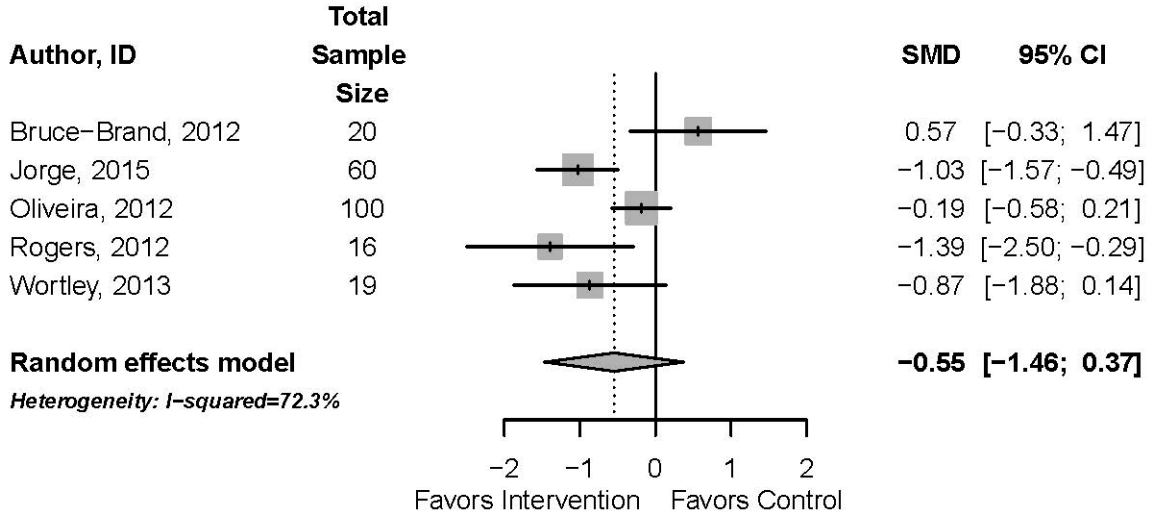


Figure notes: CI=confidence interval; SMD=standardized mean difference; WOMAC=Western Ontario and McMaster Arthritis Index

Short-term effects on function. Six RCTs met our inclusion criteria for assessing short-term effects of strength training interventions on function.[44-47, 49, 50]

The 2012 Brazilian RCT found that the 8-week strengthening program improved function compared with the educational control group based on Lequesne Index scores (MD -1.98, 95% CI -3.75, -0.21) but the difference was not reflected in WOMAC function scores.[47]

The study by Bruce-Brand reported no change in WOMAC function scores between the resistance training and control groups at 8 weeks.[44] However, three other function tests, the primary outcomes of the study, showed significant improvements from baseline to 8 weeks compared to the control group (described below).

The 2012 RCT conducted by Rogers and coworkers found that at 2 months, WOMAC function scores improved significantly compared with the control group (MD -9.62, 95% CI -19.04, -0.20),[46] and met the MCID.

The 2012 U.S. study by Wortley that compared resistance training with Tai Chi and no activity among older adults showed no significant impact of the resistance training intervention on the WOMAC function score compared with the control condition.[45]

The 2015 study by Jorge that compared resistance training with a wait-list control found no significant benefit of the program on short-term WOMAC function compared with the control group.[49]

A 2016 RCT conducted in India by Singh and coworkers that randomized 30 adults with medial compartmental knee OA to a 6-week 5-day per week hip-strengthening program or to a conventional exercise program found a significant benefit of the program on WOMAC function at 6 weeks compared with conventional exercise (MD –23.27, 95% CI –32.73, –13.81) (low RoB).[50] Pooling the results for WOMAC function for five studies showed that the effect of resistance training on short-term function was nonsignificant; heterogeneity was moderate (n=245; random effects estimate SMD -0.60, 95% CI − 1.38; 0.17; I^2 68%) (Figure 7).

Figure 7. Forest plot for short-term effects of strength training on WOMAC function score

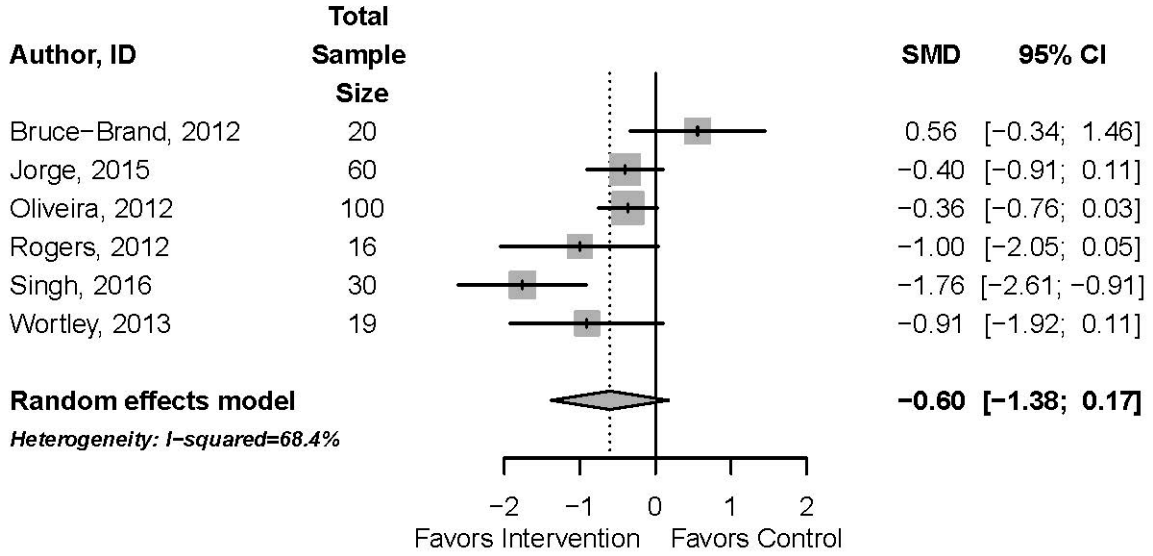


Figure notes: CI=confidence interval; SMD=standardized mean difference; WOMAC=Western Ontario and McMaster Arthritis Index

Short-term effects on other outcomes. Eight RCTs (described in nine publications) met our inclusion criteria for assessing short-term effects of strength training interventions on other outcomes of interest.[44-52]

The 2012 RCT conducted in the US by Rogers and coworkers reported the WOMAC total scores at 2 months.[46] The resistance training and control groups showed a significant between-group difference (MD -13.62, 95% CI -26.27, -0.87).

The 2012 Brazilian RCT assessed the effects of a strengthening program on two additional outcomes of interest: TUG and the physical function domain of the SF-36. The exercise group had a statistically significantly greater improvement in TUG (MD -1.80, 95% CI -2.83, -0.77) compared with the instruction group. The physical domain of the SF-36 showed no significant difference between the groups.[47, 48]

The 2012 study by Bruce-Brand reported significant improvements from baseline to 8 weeks compared to the control group in three function tests that were the primary outcomes of the study (a chair rise test, walk test, and stair climb test [$p<0.005$]) but did not find significant between-group differences in the SF-36 Physical domain.[44]

The 2012 U.S. study by Wortley compared results for the WOMAC stiffness scale, the TUG, and 6-minute walk tests between intervention groups.[45] After the 10-week intervention, participants in the resistance training group showed no between-group improvement compared with the control group on the TUG or the 6-minute walk test.

A 2014 RCT conducted in the Republic of Korea by Nam randomized 30 sedentary adults (age 60 and older) with knee OA to a program of strength-training exercises carried out on an aero step XL™ or the same exercises performed on a flat surface (3 times a week for 6 weeks) (RoB moderate).[51] At 6 weeks, a significant between-group difference was observed in total WOMAC scores (MD –2.99, 95% CI –5.48, –0.50).

The 2015 study by Jorge that compared resistance training with a wait-list control found a significant short-term benefit of the training on WOMAC total scores (MD –8.20, 95% CI –14.78, –1.62) and on the physical domain of the SF-36 (MD –8.80, 95% CI –17.26, –0. 34) but not on the 6-minute walk.[49]

The 2016 study by Singh and coworkers found a significant benefit of their hip strengthening program on 6-minute walk test performance (MD –58.30, 95% CI –85.68, –30.92).[50]

Medium-term effects on pain. Four RCTs met our inclusion criteria for assessing medium-term effects of strength training on pain.[44, 49, 52, 53]

A 2011 Australian RCT, the REACH study, randomized 54 women to a 6-month resistance training or sham training program (consisting of less intense resistance training) (RoB low).[52] The primary outcome was assessment of dynamic alignment; WOMAC scores were secondary outcomes. At the end of the intervention, WOMAC pain scores showed no significant between-group differences.[52]

The 2012 study by Bruce-Brand found no improvement in WOMAC pain scores at 14 weeks (6 weeks post intervention) in the resistance training group compared with the control group.[44]

The 2016 trial by Jorge that compared a 12-week strength training program with a weight list control found a significant benefit of the program at 12 weeks on WOMAC (MD –4.60, 95% CI –6.50,– 2.70) and VAS (MD –2.30, –3.55, –1.05) pain scores.[49]

A 2016 double-blind (participants and assessors) RCT conducted at two sites in Australia by Bennell and colleagues assessed the effect of strength training combined with pain coping skills training (PCST) compared with PCST or strength training exercises alone (RoB low).[53] This study randomized 222 individuals with moderate to severe knee OA to three 12-week treatment

programs and followed them for 12 months. Comparisons used a model that took into account the physical therapist training, baseline scores, site, and sex. The group that received strength training alone was considered the control. Overall pain was assessed on a 100mm VAS scale with a MCID set at 18mm. At 12 weeks, the strength training plus PCST group showed a significant improvement in WOMAC pain scores compared with those of the group that received only PCST (0-20 point scale, MD –1.50, 95% CI –2.50,– 0.50) but no between-group differences were seen in VAS pain. The findings for the comparison between PCST plus strength and strength alone are presented in a later section on PCST. A higher proportion of the PCST + strength training group showed global improvement in pain than did the strength training alone group (RR 1.3, 95% CI 1.1, 1.6).

Medium-term effects on function. Four RCTs met our inclusion criteria for assessing medium-term effects of strength training on pain.[44, 49, 52, 53]

The REACH study found no difference in WOMAC function between groups.[52]

The 2012 Bruce-Brand study found no difference in WOMAC physical function at 14 weeks in the resistance training group compared with the control group, however several other outcomes indicative of physical function (described below) suggest some at least sustained improvement from the first followup.[44] The 2016 trial by Jorge that compared a 12-week strength training program with a weight list control found a significant benefit of the program at 12 weeks on WOMAC function (0-68 point scale, MD –9.40, 95% CI –15.17,– 3.63) scores.[49]

The 2016 study by Bennell and colleagues found significantly greater improvements in WOMAC function at 12 weeks in the combined PCST + resistance training group compared with PCST alone (0-68 point scale MD −8.10, 95% CI −11.46, −4.74). A significantly greater proportion of participants in the PCST + resistance training group achieved global improvement in function (6 units or more) (94%) than in the PCST only group (69%, RR 1.4, 95% CI 1.2, 1.6).

Pooling the results for WOMAC function for three studies showed that the effect of resistance training on medium-term function was nonsignificant; heterogeneity was moderate (n=187; random effects estimate SMD −0.43, 95% CI −2.16; 1.30 ; I^2 69%) (Figure 8).

Figure 8. Forest plot for medium-term effects of strength training on WOMAC function score

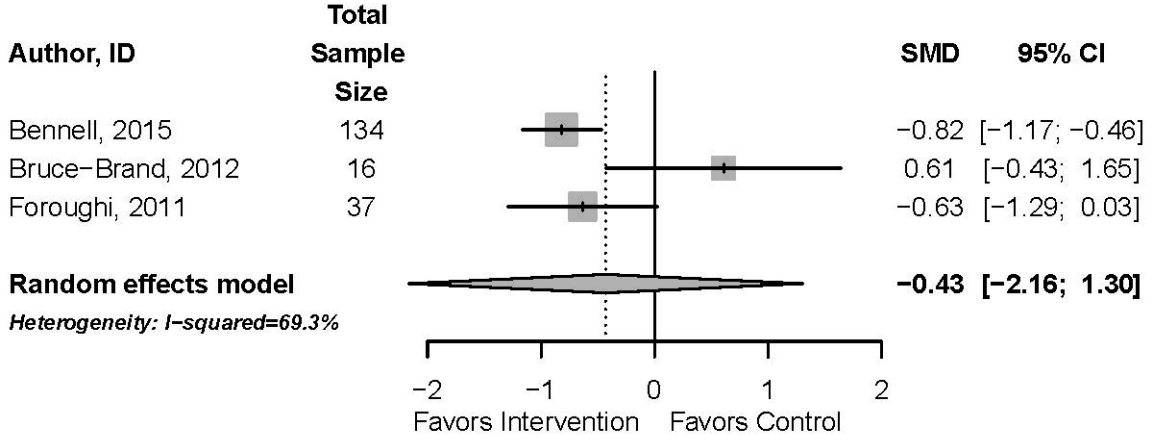


Figure notes: CI=confidence interval; SMD=standardized mean difference; WOMAC=Western Ontario and McMaster Arthritis Index

Medium-term effects on other outcomes. Three RCTs reported on medium-term effects of resistance training on additional outcomes.[44, 49, 54]

The 2011 REACH study showed a significant between-group difference in WOMAC total scores at 3 months (0-96 point scale, MD -10.40, 95% CI -20.56, -0.24).[52]

The 2012 Bruce-Brand study observed no significant difference in WOMAC stiffness scores in the resistance training group compared with the control group.[44] This study also found no effects of resistance training on the physical health domain of the SF-36 compared with the control group. However, significant short-term improvements observed in the walking test and chair rise test were maintained in the medium-term ($p<0.006$).

The 2016 Jorge study that compared a 12-week strength training program with a weight list control found a significant benefit of the program at 12 weeks on WOMAC Total (0-96 point scale MD -14.20, 95% CI -22.03, -6.37) and SF-36 physical domain (0-100 point scale MD -19.00, 95% CI -28.93, -9.07) but not on 6-minute walk scores.[49]

Long-term effects on pain. One RCT that met inclusion criteria assessed the long-term effect of a strength training intervention on pain.[53]

The 2016 study by Bennell on PCST and resistance training reported no significant improvements in VAS pain or WOMAC pain at 52 weeks in the group that received both interventions compared with PCST alone.

Long-term effects on function. One RCT that met inclusion criteria assessed the long-term effect of a strength training intervention on function.[53]

The 2016 study by Bennell reported significant improvements in WOMAC function in the PCST plus resistance training group compared with the grouping receiving PCST alone at both 32 weeks (MD −6.6, 95% CI −2.3, −10.8) and 52 weeks (MD −5.30, 95% CI −8.82, −1.78) ($p<0.01$).[53] This study also reported significant improvements in TUG performance in the PCST plus resistance training group compared with the PCST group at both 32 weeks (MD −1.10, 95% CI −1.97, −0.23) and 52 weeks (MD −1.10, 95% CI −1.84, −0.36).

Agility Training

Key Points

- It is unclear whether agility training alone has any benefit for patients with knee OA. Identified studies showed inconsistent effects across time points and outcomes.
- Agility training showed significant short-term beneficial effects on pain but not on function in 3 RCTs (low strength of evidence).
- Agility training showed no consistent beneficial effects on medium-term pain or function.
- Agility training showed no long-term beneficial effect on pain (3 RCTs) or function (2 RCTs) (low strength of evidence).

Findings

For the current review, we identified eight studies that assessed the effects of agility training.[46, 55-61] The current review defined an intervention as an agility training intervention if the study authors explicitly referred to the intervention as agility training or if they used the terms joint stabilization, or neuromuscular exercise or proprioception, or if the primary activity of the intervention (based on time spent on that activity) was aimed at improving those functions. These studies generally included several sessions per week of therapist-led individual or group exercise (including a brief period of warm-up aerobic exercise prior to the strength training period and a cool down period following the strength training) with instructions to perform some exercises at home on the other days. The details are described in the evidence table in Appendix C.

Short-term effects on pain. We identified three RCTs that met inclusion criteria and assessed the effects of a short- or medium length agility training intervention on short-term pain.[46, 57, 61]

A 2012 RCT conducted in the US by Rogers and coworkers randomized 44 adults age 50 and over to one of four 8-week home-based interventions: kinesthesia, balance, and agility (KBA) training alone, resistance training (RT) alone, a combination of KBA and RT, and a control group that received no intervention (RoB moderate).[46] At 8 weeks, WOMAC pain scores for the agility training group showed a significant between-group difference compared with those of the control group (MD -3.13, 95% CI, -5.86, -0.40).

A 2013 RCT conducted in the Netherlands by Knoop and coworkers randomized 159 adults to a 12-week program comprising knee joint stabilization therapy plus muscle strengthening or to a program of muscle strengthening alone (RoB low).[61] The first week of therapy consisted of hydrotherapy in both groups. At 6 weeks, no significant between-group differences were seen in NRS-measured knee pain. The proportion of responders (based on an MCID of 15%) was also the same in both groups: 70 percent compared with 72 percent.

A 2015 RCT conducted in Korea by Ju and colleagues randomized 14 women, 60 years or older, with knee OA to an 8-week program of proprioceptive circuit exercise or a control group (RoB unclear).[57] At 8 weeks, VAS pain scores improved significantly in the intervention group compared with the control group (1-10 cm: MD -4.00, 95% CI -5.32, -2.68).

Short-term effects on function. We identified three RCTs that met inclusion criteria and assessed the effects of an agility training intervention on short-term function.[46, 58, 61]

The 2012 Rogers study reported no significant improvements in WOMAC function at 8 weeks compared with the sham control group.[46]

A 2015 RCT conducted in Brazil by da Silva and colleagues randomized 41 participants with moderate to severe knee OA to an 8-week rehabilitation program that included mobility, functional, and balance exercises in addition to strength training or to a control condition: Both groups received self-management educational sessions (RoB moderate).[58] At 8 weeks, no between-group difference was seen in Lequesne composite scores. Both exceeded the MCID (defined by the authors as an effect size greater than 0.01).

The 2013 study by Knoop and colleagues assessed WOMAC physical function as its primary outcome.[61] At 12 weeks, no significant between-group differences were seen, and no difference in the proportion of responders (66% vs. 63%), based on an MCID of 12 percent.

Short-term effects on other outcomes. The 2015 RCT by da Silva found that at 8 weeks, the intervention group performed significantly better on the TUG (MD -2.05, 95% CI -3.12, -0.98) and the 6-minute walk (MD -50.40, 95% CI -94.26, -6.54) than did the control (education) group. This study also reported a significant difference in scores on the SF-36 Physical Function domain (MD -14.00, 95% CI -26.24, -1.76).[58]

The 2012 Rogers study reported no significant improvements in WOMAC total scores at 8 weeks compared with the control group.[46]

Medium-term effects on pain. Three RCTs reported on medium-term effects of agility training on pain.[56, 60, 61]

The 2013 3-month RCT by Knoop found a nonsignificant between-group difference in NRS pain at 3 months.[61]

A 2014 RCT conducted in Denmark by Henriksen and coworkers randomized 60 individuals with OA of the knee to a 12-week program of facility-based neuromuscular exercise therapy or to a no-attention control group (RoB Low).[56] The primary outcome was sensitivity to pressure

pain. At 12 weeks, KOOS pain, a secondary outcome, was statistically significantly improved in the intervention group compared to the control group (MD −6.80, 95% CI −12.18, −1.42)).

A 2015 RCT conducted in the US by Segal and colleagues randomized adults 60 years and older with knee OA and mobility limitations 2 to 1 to a gait-training intervention or to a usual care control group (RoB low).[60] At 6 months, no between-group differences were observed using the KOOS pain measure.

Medium-term effects on function. The 2013 RCT by Knoop found no significant between-group differences in function at 3 months.[61]

The 2014 RCT by Henriksen found no significant differences in function between the agility training and the usual care group.[56]

Medium-term effects on other outcomes. Three RCTs reported on medium-term effects of agility training on other outcomes of interest.[59, 61]

The 2013 RCT by Knoop found no significant between-group differences in timed up and go (TUG) at 3 months.[61]

A 2013 RCT conducted in Brazil by Barduzzi randomized 15 older adults (60 to 80 years) with OA of the knee to receive water based agility kinesiotherapy, land-based agility kinesiotherapy, or a control condition (RoB High).[59] The intervention consisted of 24 sessions over 4 months with a 45-day break between the 12th and 13th session. At the end of the 4-month period, the water-therapy group showed a significantly better walking speed than the control group ($p<0.007$). The land-based agility exercise group showed no between-group differences from the control group.

The 2014 RCT by Henriksen found no significant differences in KOOS quality of life scores between the agility training and the usual care group.[56]

Long-term effects on pain. Three RCTs assessed the effects of agility training on long-term pain.[55, 60, 61]

A 2011 U.S. RCT by Fitzgerald and colleagues randomized 183 individuals with knee OA to a group that received a standard exercise program with agility training for 6 months or to a group that received only the standard exercise program (RoB low).[55] NRS-assessed knee pain scores were measured at 2 months, 6 months, and 12 months, but only the 12-month measures underwent ITT analysis. No between-group differences in pain were seen.

The 2013 study by Knoop and colleagues assessed pain at 38 weeks (6 months after the end of the intervention).[61] A nonsignificant between-group difference was seen in NRS-measured pain. The proportion of responders was 72 percent for the intervention group and 57 percent for the control group, based on an MCID of 12 percent.

The 20015 U.S. RCT by Segal and colleagues that assessed the effects of gait training found no between-group differences in KOOS-estimated pain at 12 months.[60]

Long-term effects on function. Two RCTs assessed the effects of agility training on long-term function.[55, 61]

The 2011 Fitzgerald study assessed the effects of the agility training intervention on WOMAC function.[55] No between-group differences were seen.

The 2013 study by Knoop and colleagues assessed WOMAC physical function at 38 weeks after baseline (6 months after the end of the intervention).[61] At 38 weeks, no between-group differences were seen in WOMAC function, and no difference was observed in the proportion of responders (62% vs. 61%), based on an MCID of 12 percent.

Long-term effects on other outcomes. In the 2011 study by Fitzgerald and colleagues, total WOMAC scores at 12 months (10-months after the end of the intervention period) showed no differences between the agility group and the standard exercise group.[55]

General Exercise Therapy

Key Points

- General exercise programs appear to have beneficial medium-term effects on pain and function and long-term effects on pain for patients with knee OA, based on a relatively small number of heterogeneous RCTs.
    - Evidence was insufficient to assess the effects of general exercise therapy programs on short-term pain or function.
    - General exercise therapy programs had a beneficial effect on medium term pain and function, based on two RCTs (low strength of evidence).
    - General exercise therapy programs showed beneficial long-term effects on pain, based on 4 RCTs (low strength of evidence), but evidence was insufficient to assess long-term effects on function or quality of life.

Findings

For the current review, we identified six RCTs whose exercise interventions did not fit the definitions of any of the other types of exercise therapy.[62-67] These studies generally included several sessions per week of therapist-led individual or group exercise (including a brief period of warm-up aerobic exercise prior to, and a cool down period following some combination of exercises) with instructions to perform some exercises at home on the other days. One RCT compared aquatherapy to a program of similar exercises performed on the land.[63] The details are described in the evidence table in Appendix C.

Short-term effects on pain. One RCT assessed short-term effects of general exercise interventions on pain.[63, 66]

A 2016 RCT conducted in the Netherlands by de Rooij and colleagues randomized 126 adults with knee OA and at least one comorbidity to a 20-week (two sessions per week) exercise program that was individually tailored to accommodate the participants' comorbidities or to a wait list control (RoB low).[66] At 10 weeks' followup, no between group differences were seen in WOMAC pain or NRS pain measures.

Short-term effects on function. At 10 weeks' followup, the de Rooij RCT also showed no beneficial effects of the exercise intervention on WOMAC function scores.[66]

Short-term effects on other outcomes. One RCT compared the short-term effects of a general water-based exercise program to those of a land-based program of similar exercises and to a control group (Low RoB).[63] This 2010 study conducted in the Republic of Korea by Lim and colleagues, randomized 75 obese adults with knee OA to an 8-week program (3 sessions per week) of aquatic exercise, land-based exercise, or a usual care control group. At 8 weeks, neither the aquatic exercise group nor the land-based exercise group showed significant improvements in WOMAC total scores compared with the control group.

The Lim RCT also reported nonsignificant improvements in SF-36 physical domain scores in the aquatic fitness and land-based exercise groups compared with the control group.[63]

At 10 weeks, the de Rooij RCT showed no between group differences in the TUG or the 6-minute walk tests.[66]

Medium-term effects on pain. Two RCTs assessed medium-term effects of general exercise interventions on pain.[64, 66]

A 2014 RCT conducted in Canada by Rosedale and colleagues randomized 180 individuals with knee OA to an exercise group (120) or a nonexercise control group (60) (RoB low).[64] The exercise intervention that was implemented depended on the intervention participants' responses to the McKenzie System of Mechanical Diagnosis and Therapy (MDT); responders are defined as those who show knee derangements when asked to perform particular movements, and the exercises were focused on these derangements. At 3 months, the combined exercise group had significant improvements in KOOS pain scores (0-100: MD -10.00, 95% CI -15.28, -4.72) and P4 pain scores (0-40: MD -3.00, 95% CI -5.84, -0.16) compared to the control group.

At 20 weeks, the de Rooij RCT showed significant beneficial effects of the exercise program on both WOMAC (0-17 point scale, MD –1.90, 95% CI −3.28, −0.52) and NRS (0-10 point scale, MD –1.50, 95% CI −2.26, −0.74) pain scores compared with the control group. [66]

Medium-term effects on function. At 3 months, the combined exercise groups in the study by Rosedale and colleagues had significantly higher KOOS function scores (indicating improvement) than did the control group (0-100 scale: MD -9.00, 95% CI -14.28, -3.72). Comparisons are not shown for the two exercise subgroups, as they were not randomly allocated.[64]

At 20 weeks, the de Rooij RCT showed significant beneficial effects of the exercise program on WOMAC function scores (0-68 point scale, MD –5.10, 95% CI −9.81, −0.39).[66]

Medium-term effects on other outcomes. At 20 weeks, the de Rooij RCT showed significant beneficial effects of the exercise program on SF-36 physical domain scores (0-20 point scale, MD –1.90, 95% CI −3.62, −0.18) but not on TUG or 6-minute walk test scores.[66]

Long-term effects on pain. Four RCTs assessed the long-term effects of general exercise interventions on pain.[65-68]

A 2015 RCT conducted in New Zealand by Abbott and colleagues randomized 75 adults with OA of the knee to one of four interventions: 12 weekly exercise sessions, 8 weekly sessions plus four additional (booster) sessions every three months over the course of the following 9 months, exercise plus 12 manual therapy sessions, or manual therapy alone (RoB moderate).[65] The group that received 12 consecutive weekly exercise sessions was considered the control. The outcomes for the manual therapy groups are discussed below with outcomes for other manual therapy studies. Compared with 12 consecutive exercise sessions, the group that received booster exercise classes over the course of the year had significantly improved VAS pain intensity scores (1-10mm scale: MD -2.00, 95% CI –3.84, -0.16).

A 2016 RCT conducted by the same research group employed the same study design with a larger population, randomizing 300 participants to the same four interventions (Low RoB).[67] At one year, the group that received the initial 12-week intervention plus the booster sessions had significantly improved pain scores compared with the group that received only the initial exercise intervention (MD −0.60, 95% CI −0.78, −0.42).

A 2015 RCT conducted in Denmark, the CAROT trial, randomized 192 adults who had completed an intensive 4-month weight loss program to continue in a weight maintenance group, to enter an exercise program, or to receive no further interventions for 1 year (RoB low).[62] The effects of the weight loss phase of the program on outcomes of interest are reported below in the section on weight loss programs.[68] The exercise program comprised three 1-hour sessions per week of circuit training, which transitioned from group sessions to home-based sessions. Over the year, the weight maintenance group regained the least weight, followed by the control group

and the exercise group. At 1 year, no significant group differences were seen between the exercise group and the control group in VAS pain.

At 32 weeks, the de Rooij RCT continued to show significant beneficial effects of the exercise program on both WOMAC (0-17 point scale, MD –2.00, 95% CI −3.37, −0.63) and NRS (0-10 point scale, MD –1.50, 95% CI −2.26, −0.74) pain scores compared with the control group.[66]

Long-term effects on function. The CAROT trial found no between-group differences in KOOS daily function scores.[62]

At 32 weeks, the de Rooij RCT continued to show significant beneficial effects of the exercise program on WOMAC function (0-68 point scale, MD –7.90, 95% CI −12.78, −3.02) scores compared with the control group.[66]

Long-term effects on other outcomes. Four RCTs assessed the long-term effects of general exercise interventions on other outcomes.[62, 65, 66, 67]

The CAROT trial found no between-group differences in outcomes for the six-minute walk or for SF-36 physical domain scores at the end of 1 year.[62]

The Abbott RCT reported a significant difference in total WOMAC scores at 12 months between the exercise and the exercise plus booster session groups, favoring the booster session group (0-240 point scale: MD -56.10, 95% CI -92.70, -19.50).[65] Booster sessions had no significant effect on the outcomes of the TUG. In contrast, the larger follow-on study by this group found no significant effect of booster exercise sessions on WOMAC total scores (the primary outcome) at one year but did find a small but significant effect on the TUG (MD −0.60, 95% CI −0.78, −0.42).[67]

At 32 weeks, the de Rooij RCT showed significant beneficial effects of the exercise program on SF-36 physical domain scores (0-20 point scale, MD –2.50, 95% CI −4.26, −0.74) as well as on the TUG (seconds, MD –1.40, 95% CI −2.69, −0.11) and 6-minute walk test scores (meters, MD –42.30, 95% CI −82.63, −1.97).[66]

Tai Chi

Key Points

- Tai chi appears to have some short- and medium-term benefit for patients with OA of the knee, based on three small, short-term RCTs and one larger, 18-week RCT (total n=290).
    - Tai chi showed significant beneficial short-term effects on pain, comparable with those of conventional physical therapy, in one large RCT, but no significant effects in two small, brief RCTs (low strength of evidence).
    - Tai chi showed beneficial effects on short-term function compared with physical therapy and education but not compared with strength training, based on three RCTs (low strength of evidence).
    - Tai chi showed significant benefit for medium-term pain and function in 2 RCTs (low strength of evidence).
    - Evidence was insufficient to assess long-term effects of Tai chi on pain, function, and other outcomes.

Findings

Studies of Tai chi were included if they compared Tai chi to standard aerobic or strength training regimens, attention control, or treatment as usual (TAU) but not to other specialized

exercise interventions of unknown efficacy. We found three RCTs that compared the participation in Tai chi to strength training, health education classes, or treatment as usual. [45, 69, 70] One study followed patients for 10 weeks, a second did so for 21 weeks, and a third followed patients for 52 weeks.

Short-term effects on pain. Three studies reported on the short-term effects of tai chi on pain. [45, 69, 70]

In a 2013 RCT based in the US, Wortley and colleagues assigned participants to one of three trial arms for 10 weeks: resistance strength training, tai chi, or usual medication and physical activity (RoB high).[45] WOMAC pain scores decreased significantly more in the resistance training group than in the Tai chi or TAU groups over the 10-week period.

In another 2013 RCT conducted in the US, Tsai and colleagues randomized participants to 20 weeks of Tai chi or to an attention control (health education and social activities) (RoB unclear).[69] At 9 weeks, WOMAC pain scores did not decrease significantly more in the tai chi group than in the attention control group.

A 2016 RCT conducted in the US by Wang and colleagues randomized 204 knee OA patients to an 18-week intervention of Tai chi or conventional physical therapy; the first 12 weeks was conducted in a clinic and the remaining 6 weeks was to be completed at home (RoB low).[70] At 12 weeks, both the Tai chi and the conventional physical therapy groups showed comparable beneficial effects of the interventions on WOMAC pain scores.

Short-term effects on function. All three studies examined short-term effects on function.[45, 69, 70]

Wortley found that WOMAC function scores improved in the resistance training group but not in the Tai chi group compared to the TAU group.[45] Timed up and go and 6-minute walk scores also did not significantly decrease in the Tai chi group compared to changes in the other groups.

Tsai reported that at 9 weeks, treatment effects were significantly larger in the Tai chi group for WOMAC function (MD -5.54 95% CI -9.72, -1.36) and get up and go (MD -1.54, 95% CI -0.32, -2.76), but not for WOMAC stiffness, and sit to stand scores.[69]

Wang reported that at 12 weeks, both Tai chi and physical therapy improved WOMAC function scores to a comparable extent.[70]

Medium-term effects on pain. Two RCTs assessed medium-term effects on pain.[69]

In the 20-week RCT by Tsai and colleagues[70], pain decreased significantly more in the Tai chi group than in the attention control group at 21 weeks (MD -1.58, 95% CI -2.76, -0.40). At that point, pain had decreased by 2.6 points in the Tai chi group and by 1.02 points in the attention control group (p=0.006).

At 24 weeks, the Wang RCT reported that both the Tai chi and physical therapy groups experienced similar decreases in WOMAC pain scores with no significant difference between them.[70]

Medium-term effects on function. Tsai found a significant difference in WOMAC function between groups at 21 weeks (MD -5.52, 95% CI -9.70, -1.34), favoring Tai chi.[69] In addition, WOMAC stiffness significantly decreased by 1.79 points in the Tai chi group compared to only 0.22 points in the attention control group at 21 weeks (p=0.01) but not for get up and go, and sit to stand scores.

The 2016 Wang RCT showed a significant beneficial effect of Tai chi on WOMAC function scores compared with conventional physical therapy at 24 weeks (0-1700 point scale: MD −131.10, 95% CI −251.35, −10.85).

Medium-term effects on other outcomes. At 24 weeks, the Wang RCT found a significant benefit for Tai chi on SF-36 physical domain scores compared with conventional physical therapy (0-100 point scale: MD −3.70, 95% CI −6.53, −0.87) but no difference between intervention types in 6-minute walk test scores.[70]

Long-term effects on pain, function, and other outcomes. At 52 weeks, the Wang RCT continued to show no difference between Tai chi and conventional physical therapy in the long-term benefits on WOMAC pain, function, SF-36 physical domain scores, and 6-minute walk scores.[70]

Yoga

Key Points

- It is unclear whether yoga has any benefit for patients with OA of the knee, as we identified only one small RCT (n=36).

Findings

Studies of yoga were included if they compared yoga to standard aerobic or strength training regimens, a waitlist, an attention control or treatment as usual (TAU) but not other specialized exercise interventions of unknown efficacy. We found 1 RCT that compared the participation in tai chi to a waitlist control group.[71] This study followed patients for 20 weeks.

Short-term effects on pain. In a 2014 RCT based in the US, Cheung and colleagues assigned participants to either a yoga intervention or a waitlist control for 8 weeks. (Risk of bias 7/10) [71] WOMAC pain scores decreased significantly from 8.3 points to 5.8 points for the yoga group (p=0.01).

Short-term effects on function. The Cheung study also reported short-term effects on function. [71] Authors found that WOMAC function decreased from 35 points to 22 points in the yoga group, but that this drop did not significantly differ from the change see in the control group. Short Physical Performance Battery (SPPB) repeated chair stands scores significantly increased from 2.4 to 2.8 in the yoga group (p=0.03), but there was no significant change in SPPB global, balance, and eight-foot walk scores.

Medium-term effects. This study did not examine the medium-term effects of yoga.

Long-term effects. This study did not examine the long-term effects of yoga.

Balneotherapy and Mud Treatment

Key Points

- Balneotherapy had a beneficial effect on medium-term function, and a beneficial, but inconsistent effect on medium term pain across two single-blind RCTs (low strength of evidence). No studies assessed effects of balneotherapy on short- or long-term outcomes.
- Evidence was insufficient for an effect of mud (mud baths or topical mud) on short-term outcomes.

Findings

For the current review, we identified two RCTs that assessed the effects of balneotherapy, [72, 73] one RCT that tested topical application of mud,[74] and one RCT of mud bath therapy.[75] The details are described in the evidence table in Appendix C.

Balneotherapy

Short-term effects on pain, function, or other outcomes. No studies that assessed short-term effects of balneotherapy met inclusion criteria.

Medium-term effects on pain. A 2012 RCT conducted in Italy by Fiorvanti and colleagues randomized 60 adults with bilateral knee OA to treatment that consisted of daily baths in sulfate-bicarbonate-calcium water (20 minutes per treatment, 6 treatments per week for two weeks) or usual care (RoB moderate).[72] After 12 weeks followup, a significant between-group difference was observed in VAS pain scores (0-100mm: MD-42.50, 95% CI -53.67, -31.33) and WOMAC pain scores (MD -25.70, 95% CI -34.06, -17.34).

A 2014 RCT conducted in Hungary by Kulisch and colleagues randomized 77 adults with mild to moderate OA of the knee to baths in Lake Heviz (30 minutes each, 5 times a week for 3 weeks) or to similar baths in tap water (RoB moderate).[73] The water temperature was the same for both groups, 34C. At week 15, participants who received the mineral bath treatment had significantly greater changes in VAS pain scores at rest (MD -16.00, 95% CI -26.68, -5.32) and on exertion (MD -16.60, 95% CI -25.79, -7.41) than did those who bathed in tap water. WOMAC pain scores did not differ between the two groups

Medium-term effects on function. The 2012 study on balneotherapy by Fiorvanti found significant between-group differences in WOMAC function scores (MD -37.47, 95% CI -46.61, -28.33) and Lequesne scores (MD -7.50, -9.57, -5.43).[72]

The 2014 RCT by Kulisch reported a significant improvement in WOMAC function in the balneotherapy group compared to the control group at 15 weeks (MD -8.10, 95% CI -15.82, -0.38).[73]

Medium-term effects on other outcomes. The 2012 study on balneotherapy by Fiorvanti found significant between-group differences at 12 weeks for the SF-36 functional domain (MD -32.60, 95% CI -49.62, -15.58), and use of rescue pain medication (NSAIDs and acetaminophen) ($p<0.001$).[72]

The 2014 RCT by Kulisch found no difference in WOMAC stiffness scores between treatment groups at 15 weeks.[76] The study also reported significant improvements in EQ-5D measure of general HRQoL.

Long-term effects on pain, function, or other outcomes. No RCTs that assessed long-term outcomes of interest met the inclusion criteria.

Mud Bath or Mud Therapy

Short-term effects on pain. A 2009 RCT conducted in Iran by Mahboob randomized 50 participants with OA of the knee to receive topical applications of Lake Urmia mud (prepared as a gel) or a placebo gel (20 minutes per day for 30 days) (RoB unclear).[74] At the end of the intervention, no significant between-group differences were seen in WOMAC pain scores.

Short-term effects on function. The Mahboob RCT found no significant difference in WOMAC function at the end of the trial, although both groups improved significantly from baseline.[74]

Short-term effects on other outcomes. The Mahboob RCT found significantly greater improvement in stiffness for the intervention group than for the placebo group ($p<0.05$).[74]

Medium-term effects on pain. A 2015 RCT conducted in Italy by Fiorvanti and colleagues randomized 103 adults 40 to 80 years of age with bilateral knee OA, K-L grade I-III to receive daily mud bath therapy (a combination of warm (42C) mud packs prepared from local mud (15 minutes) and bathing in the warm (37C) spring from which the mud was prepared (20 minutes), in addition to their usual therapy or treatment as usual alone for 2 weeks (RoB moderate).[75]

At 6 months, the study reported a significant between-group difference in VAS pain scores (0-100 point scale: MD −15.00, 95% CI −25.63, −4.37).[75]

Medium-term effects on function. At 6 months, the Fiorvanti study found a significant difference in WOMAC function scores between the intervention and control group (0-100 point scale: MD −10.00, −15.00, −5.00).[75]

Medium-term effects on other outcomes. At 6 months, the Fiorvanti study showed significantly improved WOMAC stiffness scores for the group that received the intervention, compared with the control group.[75] This study also reported significant improvement in the SF-12 physical domain (MD −2.46, 95% CI −22.12, −2.80) and the EQ-5D (MD −0.24, variance not reported).

Long-term effects on pain. At 12 months, the Fiorvanti study reported no significant between-group differences in WOMAC pain scores or in VAS pain scores.[75]

Long-term effects on function. At 12 months, the Fiorvanti study found a significant between-group differenced in WOMAC function scores (0-100 point scale, MD −5.50, 95% CI −10.81, −0.19).[75]

Long-term effects on other outcomes. At 12 months, the Fiorvanti study showed no between-group differences in WOMAC stiffness scores.[75] The study reported no significant differences in the SF-12 physical component or the EQ-5D.

Heat, Infrared, and Therapeutic Ultrasound

Key Points

- Insufficient evidence was identified to determine whether heat or infrared have any beneficial effects on any outcomes in patients with knee OA.
- Insufficient evidence was identified to determine whether continuous or pulsed therapeutic ultrasound (U/S) have beneficial effects on any outcomes.

Findings

For the current review, we identified one RCT that assessed the effects of heat, [77] one that assessed the effects of infrared,[78] and three that assessed the effects of pulsed and continuous U/S on outcomes of interest.[79-81] The details are described in the evidence table in Appendix C.

Short-term effects on pain. For the current review we identified one RCT that assessed the effects of heat, one that assessed the effects of infrared, and two that assessed the effects of ultrasound on short-term pain outcomes.[77, 78, 80, 81]

A 2010 RCT conducted in Turkey by Yildirim and colleagues randomized 46 adults seen in a physical therapy clinic for OA of the knee to receive 4 weeks of heat treatment every other day or to continue with usual pharmacotherapy (RoB unclear).[77] WOMAC pain scores improved significantly more in the heat therapy group at 4 weeks than in the control group (0-20-point scale: MD -1.85, 95% CI -3.15, -0.55), however the intervention group was not barred from using analgesics.

A 2012 RCT conducted in Taiwan by Hsieh and colleagues randomized 72 individuals with knee OA to two weeks of infrared treatment (three times weekly) or to a passive control (RoB low).[78] At 4 weeks after baseline, no difference was seen in KOOS pain scores between the two groups.

A 2012 RCT conducted in Brazil by Carlos and colleagues randomized 30 adults 50 to 75 years of age to an 8-week intervention consisting of 4 weeks pulsed U/S plus 4 weeks exercise (strength/resistance training), 4 weeks continuous ultrasound plus 4 weeks exercise, or 8 weeks exercise alone as the control group (RoB unclear).[80] At 8 weeks, the exercise-only group showed no significant between-group differences in WOMAC or VAS pain compared with either the continuous or pulsed U/S. No difference was seen between continuous and pulsed U/S.

A 2015 RCT conducted in Turkey by Yildiz randomized 90 adults with bilateral knee OA (KL grade II-III) to receive continuous U/S, pulse U/S, or placebo U/S (5 days per week for 2 weeks) and to perform daily exercises at home (High RoB).[81] At 2 months from baseline, both continuous and pulsed U/S groups experienced significant benefit on VAS pain (0-10 point scale: MD −1.33, 95% CI −2.55, −0.11) and (MD −1.56, 95% CI −2.82, −0.30) compared with the sham control.

Short-term effects on function. The 2010 RCT by Yildirim found a significant effect of the heat therapy on WOMAC function compared with that of pharmacotherapy alone (0-68 point scale: MD -6.05, 95% CI -9.65, -2.45).[77]

The 2012 RCT by Carlos found no significant effect of continuous U/S or pulsed U/S on WOMAC function compared with exercise alone.[80]

The 2015 Yildiz RCT found a significant benefit of both the continuous and pulsed U/S on Lequesne function scores compared with the sham control group (Scale not described; MD −2.35, 95% CI −4.11, −0.59) and (MD −2.65, 95% CI −4.27, −1.03).[81]

Short-term effects on other outcomes. The 2010 RCT by Yildirim found no significant effect of the heat therapy on WOMAC stiffness compared with that of pharmacotherapy alone but did find a significant effect on SF-36 Physical function domain score in favor of the control (MD −12.61, 95% CI, −21.49, −3.73).[77]

The 2012 RCT by Carlos found no between-group differences in the effects of U/S on total WOMAC scores.[80]

Medium-term effects on pain. At 4 months, Yildiz reported a significant benefit for both continuous (MD −3.30, 95% CI −4.62, −1.98) and pulsed (MD −3.37, 95% CI −4.70, −2.04) U/S for VAS pain, compared with sham.[81]

Medium-term effects on function. Yildiz also reported improvement in function for both continuous(MD −6.28, 95% CI −8.31, −4.25) and pulsed (MD −5.71, 95% CI −7.68, −3.74) U/S, as assessed using the Lequesne.[81]

Long-term effects on pain. A 2014 RCT conducted in Turkey by Cakir and colleagues randomized 60 adults with OA of the knee to a 2-week intervention of continuous U/S, pulsed U/S, or sham U/S (RoB moderate).[79] All three groups participated in a simultaneous exercise program. At the end of 6 months, no significant differences were observed in WOMAC pain or VAS pain between either the continuous or pulsed U/S groups and the sham U/S group. All three groups experienced comparable improvement, defined as 40 percent improvement or a decrease of 8 units in the WOMAC pain score from baseline.

Long-term effects on function. The 2014 Cakir study found no difference between either the continuous or pulsed U/S group and the sham U/S group in WOMAC function at 6 months.[79]

Neuromuscular Electrical Stimulation (NMES)

Key Points

- Evidence was insufficient to assess the short-term effects of NMES combined with exercise compared with exercise alone (or NMES compared with a sham control) on pain or function, based on three RCTs.
- Evidence was insufficient to assess the medium- and long-term effect of NMES on pain and function.

Findings

Studies of NMES were included if they compared NMES to sham or to use of analgesics but not to other treatments of unclear efficacy. We identified 5 RCTs that compared NMES to a control or exercise with NMES to exercise alone.[44, 82-85] The longest followup time ranged from 6 weeks to 18 weeks from baseline.

Short-term effects on pain. Four studies reported on short-term effects of NMES treatment on pain.[44, 83-85]

A 2012 single-blind RCT conducted in Ireland by Bruce-Brand et al randomized 41 patients into three treatment groups: a group that received one 20-minute NMES session daily, 5 days per week for 6 weeks, a group that received three 30-minute home-based resistance trainings (RT) per week for 6 weeks, and a control group, which received standard care (RoB moderate).[44] WOMAC pain score at 8 weeks' followup was significantly decreased from baseline in the NMES group ($p<0.005$); however, no significant differences in pain were noted between groups after treatments.

A 2013 RCT conducted in Brazil by Imoto and colleagues randomized 100 patients into two treatment groups: a group that received NMES combined with exercise and a group that received exercise alone; both groups received the treatments twice a week, for 8 weeks, with each session lasting about 40 minutes (RoB low).[83] At 8 weeks' followup, NRS and WOMAC pain scores were significantly decreased from baseline in both NMES+ exercise and exercise groups ($p<0.0001$), whereas no significant differences between groups were found.

Another 2013 RCT conducted in Brazil by Imoto and coworkers randomized 100 patients into two groups: one that received an educational guide and strength training with NMES and one that received an educational guide and two phone calls as a control group (RoB low).[84] NRS pain scores at 8 weeks' followup were significantly decreased in the NMES group compared with the control group (MD −1.44, 95% CI −2.65, −0.23; $p<0.05$).

A 2013 RCT conducted in Israel by Elboim-Gabyzon and colleagues randomized 63 patients to receive 12 biweekly exercise-only treatments or exercise combined with NMES treatments (RoB moderate).[85] At 6 weeks' followup, VAS pain scores were significantly improved for the exercise + NMES group compared with those of the exercise-only group (MD −1.70. 95% CI −2.92, −0.42; $p<0.05$).

Short-term effects on function. Bruce-Brand and Imoto[44, 83, 84] also assessed the effects of NMES on function. At 8 weeks' followup, Bruce-Brand[44] found no significant differences in WOMAC function either from baseline or between groups; Imoto [83] reported significant decreases in WOMAC function from baseline in both NMES + exercise and exercise groups ($p<0.0001$) but no significant differences between groups. In the other 2013 RCT conducted by Imoto,[84] the NMES group showed significantly greater improvement in Lequesne index scores than did the control group (MD −2.81, 95% CI −4.53, −1.09; $p<0.05$) at 8 weeks' followup.

Medium-term effects on pain. At 14 weeks' followup, Bruce-Brand[44] found no significant between-group differences in WOMAC pain scores. Following up patients in the 2013 RCT conducted by Elboim-Gabyzon[85] for another 12 weeks, Laufer[82] reported that the greater improvement in VAS pain scores remained for those who received exercise combined with NMES (−1.90, 95% CI −3.25, −0.55; p<0.05)(RoB moderate).

Medium-term effects on function. Bruce-Brand[44] assessed the medium-term effects of NMES on function. At 14 weeks' followup, WOMAC function scores were significantly decreased from baseline in the NMES group (p<0.005) while no differences were seen between the NMES and RT groups or between the NMES and control groups.

Long-term effects. No studies reported on long-term effects of NMES.

TENS

Key Points

- TENS showed a small but significant beneficial short-term effect on pain compared with sham controls based on pooled analysis of four RCTs (moderate strength of evidence), but no benefit for short-term function or other outcomes (low strength of evidence). The beneficial effect on pain was not sustained over the medium term.

Findings

For the current review, we identified four RCTs that assessed the effects of TENS.[86-89] The details are described in the evidence table in Appendix C.

Short-term effects on pain. Four RCTs assessed the short-term effects of TENS on pain [86-89]

A 2010 RCT conducted in Germany by Gschiel and colleagues randomized 45 participants with uni- or bilateral OA of the knee to receive TENS or sham TENS therapy, 30 minutes twice a day for 3 weeks (RoB moderate).[86] At week 5, no significant difference was observed in WOMAC pain between the active and sham treatment.

A 2012 RCT conducted in Turkey by Atamaz and colleagues randomized 74 participants to TENS or sham TENS treatment 20 minutes per day, 5 times a week for 3 weeks (RoB low).[87] All participants also participated in an exercise program, 3 times per week for 3 weeks and received a single educational session. At week 4, no between-group differences were seen in VAS pain scores or WOMAC scores.

A 2014 RCT conducted in the UK by Palmer and colleagues randomized 224 participants with knee OA to receive self-administered TENS plus exercise, sham TENS plus exercise, or exercise alone for 6 weeks (RoB low).[88] All groups received education sessions. The primary outcome was WOMAC function (below). At 6 weeks, a significant between-group difference was seen in WOMAC pain (MD-2.00, 95% CI -3.46, -0.54) between the TENS and the sham TENS groups.

A 2016 RCT conducted in Turkey by Inal and colleagues randomized 93 women with symptomatic knee OA to two weeks (5 sessions per week) of low-frequency TENS, high-frequency TENS, or sham TENS (Unclear RoB).[89] Although the study authors reported significant improvements in pain immediately after treatment (at 2 weeks), no significant differences were reported in VAS pain at rest or WOMAC pain scores at 6 weeks among the low frequency, high frequency, and sham groups.[89]

A random effects pooled estimate for all four studies showed a small significant effect of TENS treatment on WOMAC pain compared with a sham control that did not exceed the prespecified MCID (pooled effect size -0.31, 95% CI−0.56, −0.06) (Figure 9).

Figure 9. Forest plot for short-term effects of TENS on WOMAC pain score

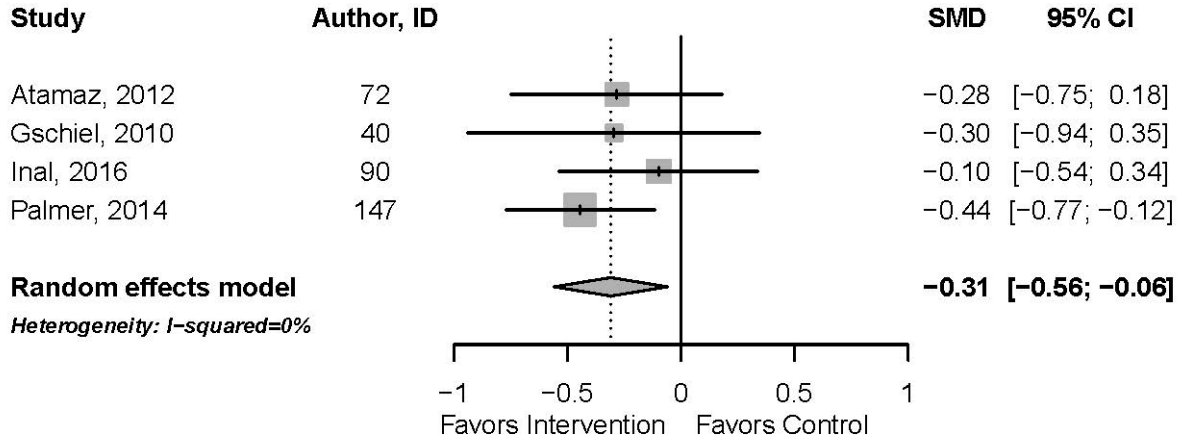


Figure notes: CI=confidence interval; SMD=standardized mean difference; WOMAC=Western Ontario and McMaster Arthritis Index

Short-term effects on function. Three of the RCTs reported short-term effects of TENS on WOMAC function.

At 4 weeks, Atamaz[87] found no significant difference between groups in WOMAC function scores.

At 6 weeks, Palmer[88] found no difference in WOMAC function scores for TENS vs sham TENS. The percent of participants in the active TENS group who achieved a clinically significant improvement in function was lower than that for the sham TENS group or the exercise group (RR 1.08, 95% CI 0.69, 1.69).

At 6 weeks, Inal[89] found no significant difference in WOMAC function between either the high or low-frequency TENS treated and the sham-treated groups.

Short-term effects on other outcomes. At 4 weeks, Gschiel[86] reported no difference in total WOMAC scores between the TENS and sham-TENS treated groups.

At 6 weeks, Palmer[88] reported no difference in WOMAC stiffness or total WOMAC scores between TENS and sham-TENS groups.

At 6 weeks, Inal[89] found no significant difference in WOMAC total scores between either the high or low-frequency TENS treated and the sham-treated groups.

Medium-term effects on pain. Two RCTs reported on medium-term effects on pain.[87, 88] At 6 months, (4 months after the intervention), Atamaz[87] reported no between-group differences in VAS pain or WOMAC pain scores.

Palmer[88] reported no between-group differences in WOMAC pain between active- and sham TENS groups at 6 months.

Medium-term effects on function. Two of the RCTs reported medium-term effects of TENS on WOMAC function.

At 6 months, although improvements persisted from 4 weeks, Atamaz[87] found no significant difference between groups in WOMAC function scores.

At 6 months, Palmer[88] found no between-group differences in WOMAC function scores for TENS vs sham TENS.

Medium-term effects on other outcomes. At 6 months, Palmer[88] reported no difference in WOMAC stiffness or total WOMAC scores between TENS and sham-TENS groups.

Pulsed Electromagnetic Field (PEMF)

Key Points

- PEMF had a statistically nonsignificant beneficial effect on short-term pain based on a pooled analysis of three RCTs (low SoE).[90-92]
- Evidence is insufficient to assess the effects of PEMF on short-term function or other outcomes.

Findings

Studies of PEMF were included if they compared PEMF to sham or to use of analgesics but not to other potential therapeutic agents of unclear efficacy. We identified three RCTs that compared the use of PEMF to that of a sham control.[90-92] The longest followup times were 42 days and 4 weeks from baseline.

Short-term effects on pain. A 2013 double-blind RCT conducted in the US by Nelson and colleagues randomized 34 patients into two treatment groups: a group that received PEMF and a group that received sham control (RoB low).[90] Mean maximum VAS pain scores at 14 days' and 42 days' followup were significantly decreased from baseline and from that of the control group in the active treatment group (VAS 0-10 scale: MD −1.92, 95% CI −2.35, −1.49) (exceeding a MCID of −0.9).

A 2015 double-blind RCT conducted in Turkey by Dundar and colleagues randomized 40 patients to receive PEMF or sham PEMF; each group also received conventional physical therapy (including hot pack, ultrasound, transcutaneous nerve stimulation (TENS) and isometric knee exercise)(RoB moderate).[91] At 4 weeks' followup, no significant difference in VAS or WOMAC pain scores was found between the active and control groups.

A 2016 RCT conducted in Italy by Bagnato and colleagues randomized 66 knee OA patients to receive 1 month of daily PEMF treatment (12 hours per day, usually during sleep). This study found a significant beneficial effect of PEMF on WOMAC pain scores at 1 month compared with a sham control (MD −5.20, 95% CI −9.72, −0.68) (low RoB).[92]

A random effects pooled estimate for all four studies showed a nonsignificant short-term effect of PEMF treatment on VAS pain compared with a sham control; heterogeneity was moderately high (pooled effect size −12.44, 95% CI −34.41, 9.54; I^2 76%) (Figure 10).

Figure 10. Forest plot for short-term effects of PEMF on VAS pain score

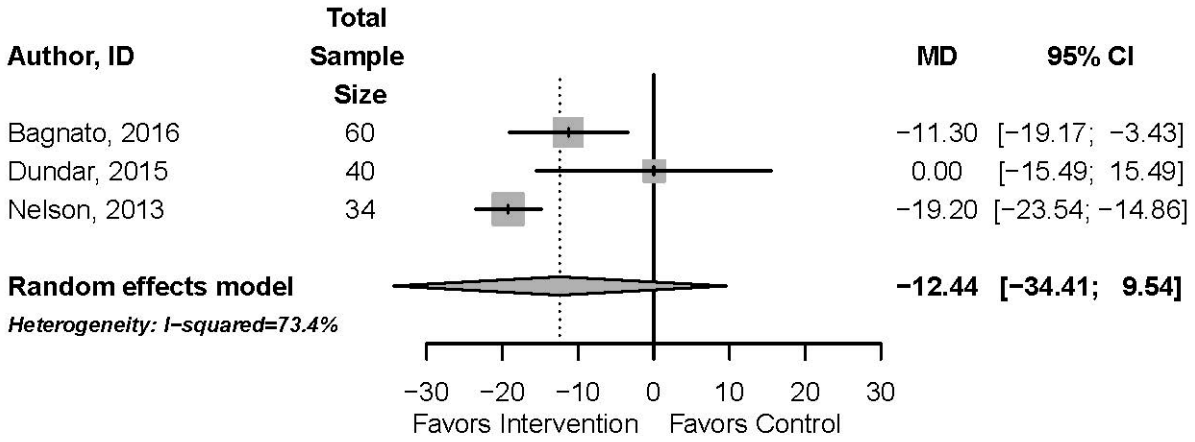


Figure notes: CI=confidence interval; SMD=standardized mean difference; VAS=Visual Analog Scale

Short-term effects on function. The Bagnato RCT identified no significant beneficial effect of PEMF on WOMAC function at 1 month, compared with the sham control (MD −8.00, 95% CI −26.32, 10.32).[92]

Short-term effects on other outcomes. The Bagnato RCT identified no beneficial effect of PEMF on WOMAC total scores or on the SF-36 physical domain.[92]

Longer term effects. No studies reported on longer term effects of PEMF.

Whole-Body Vibration

Key Points

- It is unclear whether WBV has a beneficial effect on patients with knee OA, as pooled analysis showed inconsistent effects on pain and function.
- WBV combined with exercise demonstrated no short-term beneficial effects on pain compared with exercise performed on a stable surface or not combined with WBV, based on three RCTs (low strength of evidence).
- Evidence is insufficient to draw conclusions on short-term effects of WBV on function or other outcomes.
- WBV-based exercise showed no beneficial medium-term effects on pain, based on pooled analysis of four RCTs (low strength of evidence).
- WBV-based exercise showed a small but statistically significant medium-term beneficial effect on WOMAC function, based on pooled analysis of 4 RCTs (n=180; SMD −0.26, 95% CI −0.45, 0.06) (low strength of evidence) that did not meet the MCID of -0.37. However no beneficial medium-term effect was observed on the 6-minute walk, based on pooled analysis of four RCTs (low strength of evidence).

Findings

For the current review, we identified seven RCTs that assessed the effects of WBV. The details are described in the evidence table in Appendix C.[93-99]

Short-term effects on pain. We identified three RCTs that assessed the short-term effects of exercise done while undergoing WBV on measures of pain or exercise followed immediately by WBV.[95, 98, 99]

A 2013 RCT conducted in South Korea by Park randomized 44 women age 50 and over to two groups (RoB unclear).[98] The intervention group received 2 months of WBV (three times per week for 20 minutes each) and was taught a set of exercises to perform at home. The control group received only the home-based exercise instruction. At 2 months, the experimental group reported significantly less NRS-assessed pain than did the control group (MD −2.00, 95% CI −3.77, −0.23).

A 2015 RCT conducted in China by Wang randomized 99 individuals (age 40 to 65) to a strength-training program conducted with WBV or a control strength training program on a stable surface (30 minutes per day, 5 days per week for 6 months) (RoB low).[95] At 1 month, no significant between-group difference was observed in VAS pain scores (10 cm scale, MD −0.50, 95% CI −1.10, 0.10) or WOMAC pain scores (maximum 20 points, MD −0.45, 95% CI -1.40, 0.50).

A 2016 RCT conducted in Iran by Bokaeian and colleagues randomized 28 individuals with knee OA to 8 weeks of strength training sessions (three sessions per week) followed by WBV or without WBV (High RoB).[99] At 8 weeks, no significant difference was reported in VAS pain scores between the groups.

Short-term effects on function. One RCT assessed the short term effects of WBV on function.[95] At 1 month followup, Wang found no between-group differences in WOMAC function scores (maximum 68 points, MD 0.21, 95% CI −2.63, 3.05)

Short-term effects on other outcomes. The study by Park showed that WOMAC total scores decreased in both the WBV plus exercise and exercise-only groups, with no difference between groups (MD −3.36, 95% CI −10.01, 3.29).[98]

Wang[95] identified no between-group differences at 1 month in performance on the 6-minute walk test (MD −3.14, 95% CI −333.26, 326.98), TUG (MD −0.26, 95% CI −1.2, 0.70) or in SF-36 physical domain scores (MD −1.89, 95% CI −5.03, 1.25).

At 8 weeks, Bokaeian found no significant difference in total WOMAC scores between participants who received WBV after strength training sessions and those who received no WBV.[99]

Medium-term effects on pain. Four RCTs conducted by two groups reported medium-term effects of WBV on pain.[93, 95-97]

A 2011 RCT conducted in Brazil by Avelar randomized 23 adults age 60 and older with knee OA to a 12-week program of strength training (3 times per week for 3 months) conducted with WBV or without WBV on a stable surface (RoB unclear).[93] At 3 months, no between-group difference was seen in the WOMAC pain score (MD 24.00, 95% CI −60.64, 108.64).

A 2012 RCT conducted in Brazil by Simao randomized 32 individuals, 60 years of age or older, to a strength training program (3 times per week for 3 months) conducted with WBV, a strength training program without WBV, or a no-activity control group (RoB moderate).[97] At 3 months, neither the WBV group nor the squat training alone group showed differences in WOMAC pain compared with the control group (MD 0.00, 95% CI −98.49, 98.49; MD −25.00, 95% CI −118.39, 68.39, respectively), and they did not differ from each other (MD 25.00, 95% CI -93.83, 143.83).

At 6 months, Wang[95] reported a significant between-group difference in VAS pain scores (MD −0.71, 95% CI −1.21, −0.21) and in WOMAC pain scores (MD −2.49, 95% CI −3.53, −1.45).

Another RCT by the same group randomized 39 individuals with medial knee OA to a pilot trial of the same program, a strength-training program conducted with WBV or a control strength

training program on a stable surface (30 minutes per day, 5 days per week for 4 months) (RoB low).[96] At 4 months, no between-group differences were observed in VAS pain scores (MD −0.60, 95% CI −1.39, 0.19) or WOMAC pain scores (MD −0.10, 95% CI −2.17, 1.97).

A random effects meta-analysis of WOMAC pain scores for these four RCTs showed no significant improvement in WOMAC pain scores with whole-body vibration compared with a control condition (SMD −0.20, 95% CI −1.12, 0.71) (Figure 11).

Figure 11. Forest plot for medium-term effects of whole body vibration on WOMAC pain score

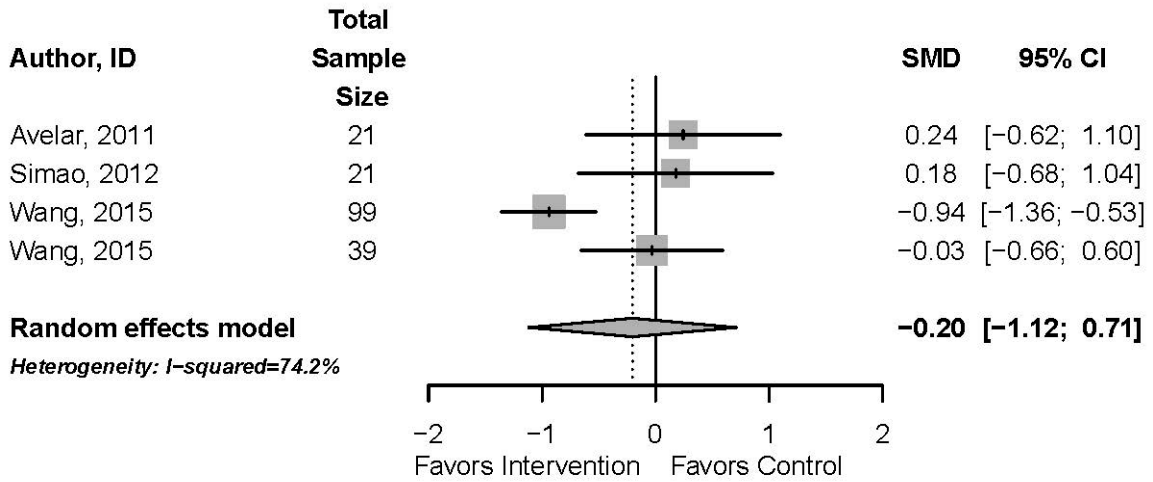


Figure notes: CI=confidence interval; SMD=standardized mean difference; WOMAC=Western Ontario and McMaster Arthritis Index

Medium-term effects on function. At 3 months, the 2011 RCT by Avelar reported no between-group difference in WOMAC function scores (MD −59.00, 95% CI −373.43, 255.43).[93]

The 2012 RCT by Simao also reported no differences between the WBV group and the exercise only group in WOMAC function (MD −122.50, 95% CI −551.90, 306.90) and no between-group differences (MD −122.5, 95% CI −551.9, 306.9).[97]

At 6 months, Wang[95] reported no between-group difference in WOMAC function scores (MD −2.63, 95% CI −5.63, 0.37) and a small but significant improvement in Lequesne scores (MD −1.19, 95% CI −2.30, −0.08).

At 4 months, Wang[96] reported no between-group differences in WOMAC function scores in the participants with medial knee OA (maximum WOMAC function score 68 points, MD −0.60, 95% CI −4.78, 3.58).

A random effects meta-analysis of WOMAC function scores for these four RCTs showed a small but significant improvement with whole-body vibration compared with a control condition (n=180, SMD −0.26, 95% CI −0.45, −0.06 (Figure 12).

Figure 12. Forest plot for medium-term effects of whole body vibration on WOMAC function score

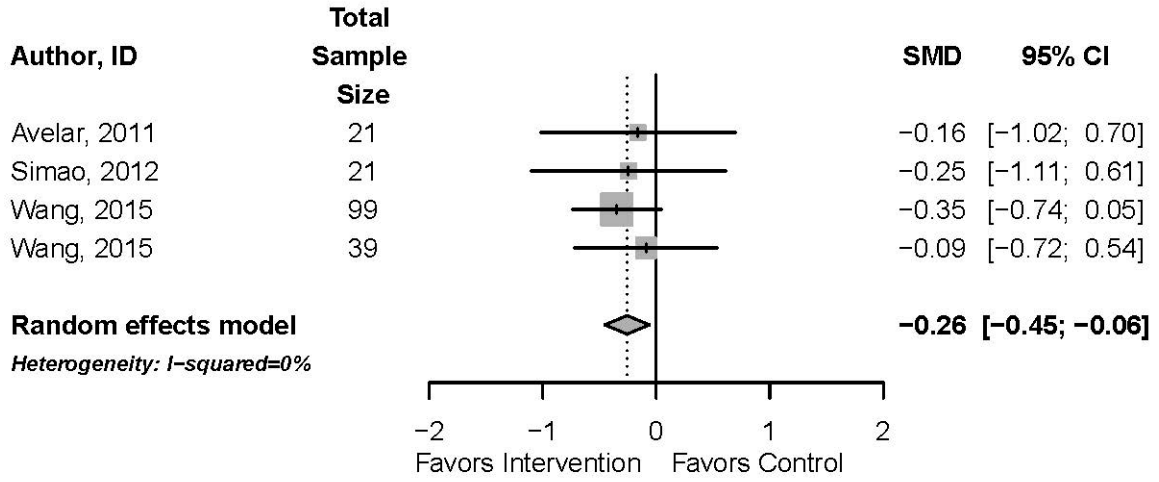


Figure notes: CI=confidence interval; SMD=standardized mean difference; WOMAC=Western Ontario and McMaster Arthritis Index

Medium-term effects on other outcomes. At 3 months, Avelar reported no significant between-group differences in the 6-minute walk test or the TUG between the WBV group and the stable strength training group.[93]

Simao reported no significant between-group differences in WOMAC stiffness scores or the 6-minute walk test between the WBV group and the control (MD −8.00, 95% CI −56.10, 40.10) and no between-group differences.[97]

At 6 months, Wang[95] reported a significant between-group difference in the 6-minute walk (MD −77.07, 95% CI −119.18, −34.96) and the TUG (MD −3.01, 95% CI −3.92, −2.10).

A 2015 RCT conducted in Italy by Rabini and colleagues randomized 50 adults (age 60 or over) to receive focal muscle vibration or a sham treatment, 3 treatments per day for 3 days (RoB low).[94] At 6 months' follow-up, significant between-group differences were observed in total WOMAC scores (MD −19.04, 95% CI −27.43, −10.65).

A random effects meta-analysis of 6-minute walk distances for these four RCTs showed no significant improvement in distances walked with whole-body vibration compared with a control condition; heterogeneity was moderately high (n=180; MD −31.17, 95% CI − 82.60, 20.26; I^2 76%) (Figure 13).

Figure 13. Forest plot for medium-term effects of whole body vibration on 6-minute walk distance

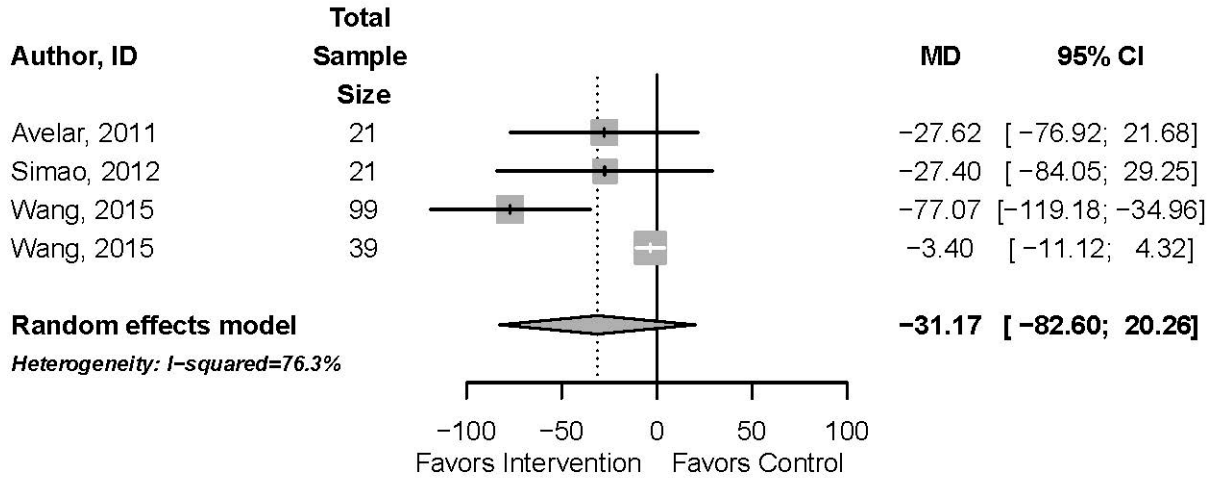


Figure notes: CI=confidence interval; MD=mean difference;

Orthoses (Knee Braces, Shoe Inserts, and Specially Designed Shoes)

Key Points

- It is unclear whether knee braces or other orthoses have a beneficial effect on patients with knee OA. Only a small number of RCTs on braces were identified, and studies of shoe inserts and specially designed shoes showed inconsistent effects across time points and outcomes.
- Knee Braces: Evidence was insufficient to determine whether custom knee braces had significant beneficial effects on any outcomes.
- Shoe Inserts showed no consistent beneficial effects across outcomes or follow-up times.
  - Custom shoe inserts had no consistent beneficial short-term effects on pain (based on four RCTs), function (three RCTs), or WOMAC total scores (pooled analysis of three RCTs) (low strength of evidence).
  - Shoe inserts showed no statistically significant beneficial effects on medium-term WOMAC pain (based on pooled analysis of three RCTs) or medium-term function (based on four RCTs) (low strength of evidence).
  - Evidence was insufficient to determine long-term effects of shoe inserts on pain, but they showed no benefit for long-term function (low strength of evidence).
- Custom shoes: Evidence was insufficient to assess medium- or long-term effects on pain or function.
- Cane Use: Insufficient evidence exists to assess the benefit of cane use on pain, physical function, and quality of life.

Findings

For the current report, we identified three RCTs on braces, eight RCTs on shoe inserts, , four RCTs on footwear, and one RCT on cane use that met inclusions criteria. The details are described in the evidence table in Appendix C.

Braces

Short-term effects on pain. A 2015 RCT conducted in the UK by Callaghan and colleagues randomized 126 individuals (40−70 years) with patellofemoral OA to the use of a patellar tracking brace or no brace daily for 6 weeks (brace use averaged 7 hours per day) (RoB moderate).[100] At 6 weeks, significant between-group differences were seen in pain measured using the VAS (0−10 cm) (MD −1.30, 95% CI −2.01, −0.59) and the KOOS (MD −5.70, 95% CI −10.76, −0.64).

Medium-term effects on pain. A 2015 RCT conducted in the US by Cherian and colleagues randomized 59 adults with moderate to severe (end-stage) knee OA to a custom pneumatic brace or to usual care; the brace group also underwent gait training 3 times a week for 6 weeks (RoB unclear).[101] At 3 months, a significant decrease in VAS pain (0−10cm scale) was observed in the brace group compared with the TAU group (MD −2.30, variance not reported).

Long-term effects on pain. A 2011 RCT conducted in Iran by Sattari and Ashraf randomized 60 patients with medial compartment knee OA (35−65 years of age) to receive a custom 3-point valgus knee support, or lateral wedge insoles, or TAU (RoB unclear).[102] At 9 months, significant differences were seen in VAS pain scores between the brace group and the TAU group favoring the braces (MD −2.80, 95% CI −3.58, −2.02). Among the brace group, 17 of 20 reported significant pain relief.

Shoe Inserts

Short-term effects on pain. Four RCTs assessed the short-term effects of orthoses on pain.[103-106]

A 2008 RCT conducted in Brazil by Rodrigues that was cited in the 2012 SR but whose data were not included in the analyses randomized 30 women with valgus knee OA to receive and wear a medial 8-mm insole or a neutral insole for 8 weeks (RoB moderate).[103] At 8 weeks, significant between-group differences were seen in VAS pain with movement (MD −2.20, 95% CI −4.04, −0.36) but not at rest.

A 2009 RCT conducted in Turkey by Koca randomized 37 women with moderate knee OA to receive and wear 6mm wedge insoles or no insoles. Both groups attended an exercise program (RoB unclear).[104] At 1 month, significant between-group differences were observed in WOMAC pain (MD −3.14, 95% CI −5.96, −0.32) but not in VAS pain at rest or during movement.

A 2014 RCT conducted in Iran by Hatef randomized 118 adults with mild to moderate medial knee OA to wear lateral wedged insoles (5 degrees) or neutral wedged insoles for 2 months (RoB moderate).[105] At 2 months, pain measured on a 0−100mm VAS showed significant between-group differences (MD−23.05, 95% CI −28.34, −17.76); pain reduction was significant in women but not in men. The likelihood of experiencing a reduction in pain to mild (RR 0.13, 95% CI 0.05, 0.36) or none (RR 0.23, 95% CI 0.03, 2.03) was also assessed and found to be greater in the lateral wedge group.

A 2015 RCT conducted in Brazil by Campos randomized 58 adults with medial knee OA to wear lateral wedge insoles with subtalar strapping or a neutral wedge insole with strapping, bilaterally, for 6 months (RoB low).[106] At 2 months, no between-group differences were seen in VAS pain or WOMAC pain measures.

Short-term effects on function. Three RCTs were identified that assessed short-term effects of insoles on function.

At 2 months, Rodrigues' RCT showed a nonsignificant between-group difference in function, as assessed using the Lequesne test (however, the between-group difference in improvements

from baseline to followup was significant, p<0.002).[103] In addition, 100 percent of participants in the medial insole group showed clinically meaningful improvements in function, compared with 78.5 percent of the neutral insole group (RR 0.79, 95% CI 0.59, 1.06).

At 1 month, the 2009 RCT by Koca showed a significant between-group difference in WOMAC function scores in favor of the insole group (MD −10.06, 95% CI −19.68, −0.44).[104]

At 2 months, Campos reported no between-group differences in Lequesne scores.[106]

Short-term effects on other outcomes. Three RCTs assessed the effects of insoles on total WOMAC scores.

Rodrigues reported no between-group differences in total WOMAC scores at 2 months.[103] At 1 month, Koca found a significant impact of insole wear on total WOMAC scores (total possible scores not reported) (MD −15.16, 95% CI −28.42, −1.90).[104] At 2 months, Campos also reported no between-group differences in total WOMAC scores.[106]

A random-effects meta-analysis of the three trials showed no significant short-term effect of orthotic use on WOMAC total scores (n=131; SMD −0.37, 95% CI −1.26, 0.53) (Figure 14).

Figure 14. Forest plot for short-term effects of orthotics on WOMAC total score

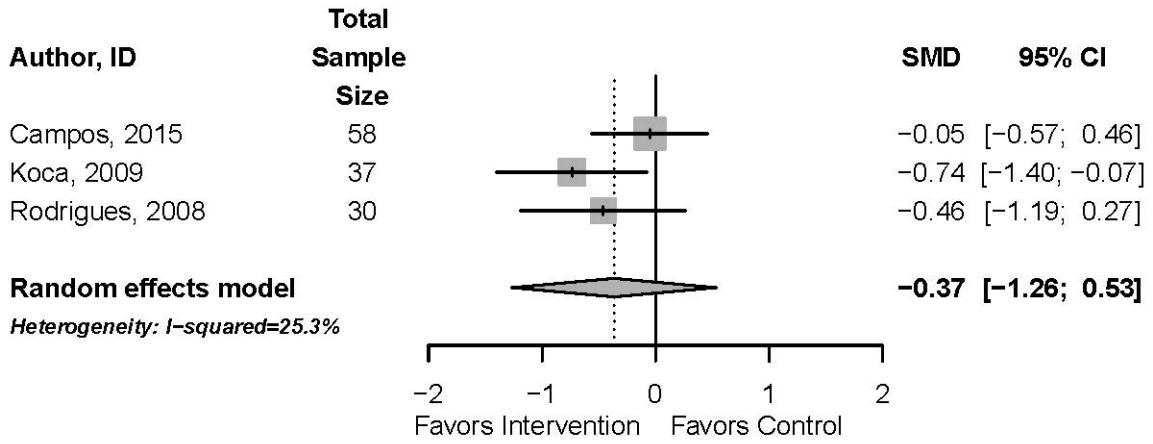


Figure notes: CI=confidence interval; SMD=standardized mean difference; WOMAC=Western Ontario and McMaster Arthritis Index

Medium-term effects on pain. Three RCTs assessed the medium-term effects of insole wear on pain.[104, 106, 107]

At 6 months, Campos found no between-group differences in WOMAC or VAS pain scores.[106]

At 3 months, Koca found no between-group differences in any measure of pain using the VAS but did find a small significant difference in favor of the wedge insole for WOMAC pain (MD −4.02, 95% CI −6.79, −1.25). [104]

A 2006 RCT conducted in the US as a dissertation project by Wallace randomized 36 adults age 30 or older with moderate-to-severe medial knee OA to wear a lateral 7-degree wedge insole or a neutral insole for 3 months (RoB unclear).[107] At 3 months, Wallace reported a significant between-group difference in VAS pain on descending stairs (0−100mm scale; MD −15.10, 95% CI −25.69, −4.51) but no differences in walking pain or WOMAC pain scores.

A random-effects meta-analysis of the three trials showed no significant medium-term effect of orthotic use on WOMAC pain scores; heterogeneity was moderate (n=131; SMD -0.48, 95% CI −1.64; 0.69; I^2 58%) (Figure 15).

Figure 15. Forest plot for medium-term effects of orthotics on WOMAC pain score

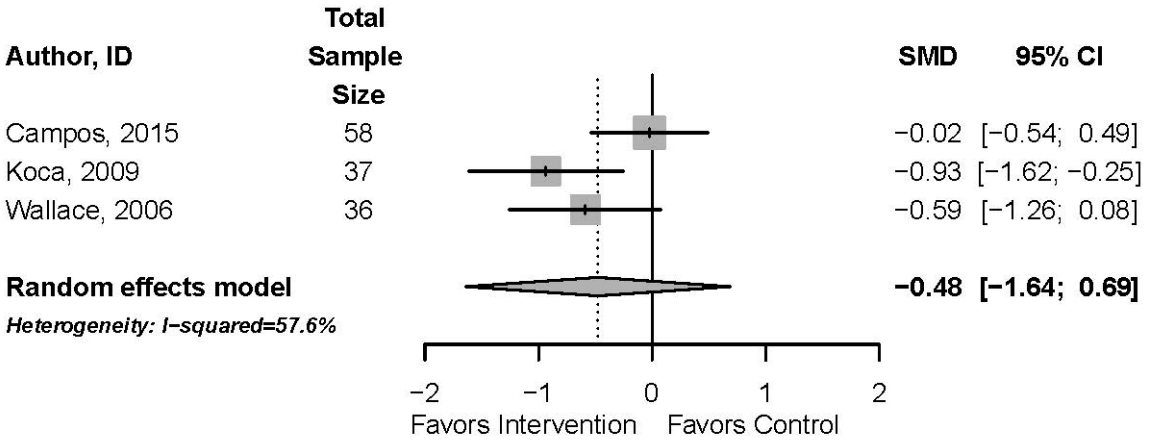


Figure notes: CI=confidence interval; SMD=standardized mean difference; WOMAC=Western Ontario and McMaster Arthritis Index

Medium-term effects on function. Four RCTs assessed medium-term effects of insoles on function.[104, 106-108]

At 3 months, Koca reported a significant between-group difference in WOMAC function in favor of the lateral insoles (MD −11.78, 95% CI −21.18, −2.38).[104]

Wallace found no significant difference in WOMAC function scores at 3 months.[107]

A 2006 RCT conducted in Japan by Toda and Tsukimura that randomized 61 women with varus deformity knee OA to lateral wedged insoles with subtalar strapping or traditional in-shoe wedged insoles for 2 years found no between-group difference in function as assessed at 6 months using the Lequesne tool (RoB moderate).[108]

At 6 months, the RCT by Campos also found no between-group differences in Lequesne function measures between the lateral-wedged insole group and the neutral insole group.[106]

Medium-term effects on other outcomes. At 3 months, Koca reported a significant between-group difference in WOMAC total scores in favor of the lateral insoles (MD −17.68, 95% CI −30.37, −4.99).[104]

Long-term effects on pain. Two RCTs assessed long-term effects of insoles on pain.[102, 109]

A 2011 RCT conducted by Bennell and colleagues in Australia randomized 200 individuals 50 and over with knee OA to a 5-degree lateral wedged insole or a neutral insole to be worn daily 12 months (RoB low). The authors reported no between-group differences in WOMAC pain at 12 months, and the decreases did not achieve minimum clinically important difference.[109]

The 2011 RCT by Sattari that assessed the effects of a knee brace on pain also assessed the effects of lateral wedged insoles compared with the control group.[102] At 9 months, the group assigned insoles had a significant improvement in VAS pain compared with the control group (MD −1.60, 95% CI −2.31, −0.89).

Long-term effects on function. Two RCTs assessed long-term effects of insoles on function.[108, 109]

The 2006 RCT conducted by Toda compared the effects of the wedge with subtalar strapping to that of the shoe insert on Lequesne-assessed function at 2 years. Although the group that wore the insole with the subtalar strap showed a small but significant improvement in function from baseline, the group that wore the inserted insole did not. No significant between-group differences were observed.[108]

The 2011 RCT by Bennell assessed WOMAC function as a secondary outcome, finding no between-group differences at 1 year.[109]

Footwear

For the current review, we identified five RCTs that assessed the effects of therapeutic footwear on measures of pain or function.

Short-term effects on pain, function, and other outcomes. No studies that met inclusion criteria assessed short-term effects of footwear on outcomes of interest.

Medium-term effects on pain. Four RCTs were identified that assessed medium-term effects of footwear on pain.[110-113] Only two studies reported usable data.[112, 113]

A 2013 RCT conducted in Brazil by Goldenstein-Schainberg and colleagues randomized 24 women with moderate knee OA to wear flexible, nonheeled ("minimalist") Moleca® footwear or normal footwear for at least 6 hours a day for 6 months (RoB unclear).[110] No data were provided in the conference proceedings that reported the findings. A significant between-group difference was seen in WOMAC pain scale scores at 6 months in favor of the minimalist shoe (p=0.01).

A second 2013 RCT conducted in Brazil by the same group randomized 28 women to the minimalist shoe or normal footwear for the same time period (RoB unclear).[111] At the end of 6 months, a between-group difference was seen in decreases in WOMAC pain scores favoring the minimalist shoe (MD −44.00, variance not reported).

A 2015 RCT conducted in Brazil by the same group randomized 56 women (60 to 80 years of age) with moderate knee OA to wear flexible, nonheeled ("minimalist") Moleca® footwear or normal footwear for at least 6 hours a day for 6 months (RoB low).[112] At 6 months, a significant between-group difference was observed in WOMAC pain (MD −38.60, 95% CI, −41.22, −35.98).

A 2010 RCT conducted in the US by Erhart and colleagues randomized 79 adults with medial knee OA to wear a variable stiffness walking shoe or a constant stiffness shoe bilaterally for 6 months (RoB moderate).[113] The between-group difference in mean WOMAC pain scores did not achieve statistical significance. The proportion of patients in the intervention group who met the MCID was significantly greater than that of the control group (RR 0.49, 95% CI 0.31, 0.79).

Medium-term effects on function. The 2015 RCT by Trombini-Souza found a significant between-group difference in WOMAC function (68-point scale, MD −43.8, 95% CI −52.70, −34.90) and Lequesne scores (24-point scale, MD −4.20, 95% CI −6.29, −2.11) at 6 months, favoring the minimalist footwear.[112]

Medium-term effects on other outcomes. Two RCTs reported medium-term effects of shoes on other outcomes,[112, 113] although only one reported the actual data.[112]

The 2010 RCT by Erhart reported no significant between-group difference in WOMAC total scores at 6 months.[113]

The 2015 RCT by Trombini-Souza found a significant beneficial effect of the intervention on WOMAC total scores (0-96 point scale, MD −43.20, 95% CI −55.77, −30.63) but no significant between-group differences in 6-minute walk distances.[112]

Long-term effects on pain. One RCT was identified that assessed long-term effects of a therapeutic shoe on pain.[114]

In a follow-up to their assessment of variable-stiffness walking shoes,[113] Erhart and colleagues assessed the effects of the shoes on pain at 1 year (RoB 8/10).[114] WOMAC pain scores were significantly decreased from baseline for both groups, with no significant between-

group differences (MD −1.00, variance not reported). Disease severity, as indicated by K-L score, did not affect response to the intervention.

Canes

One 2012 RCT conducted in Brazil by Jones randomized 64 patients with knee OA to 2 months of daily cane use or no cane use (RoB low).[115] At 2 months, a significant between-group difference in VAS pain (0−10cm, MD −2.11, 95% CI −2.83, −1.39) was observed, favoring cane use. Significant between−group improvements were also seen in Lequesne assessments of function (MD −2.34, 95% CI −4.34, −0.72) and SF-36 physical domain scores (0−100 points, MD −9.06, 95% CI −17.81, −0.31), but not WOMAC total scores (0−96 points, MD −1.06, 95% CI −8.87, 6.75).

Manual Therapy (Including Massage and Acupressure)

Key Points

- It is unclear whether manual therapies have any benefit for patients with knee OA beyond the effects of exercise alone. Across nine RCTs, benefits were inconsistent across time points and outcomes. Pooled analysis showed no statistically significant effect on short term pain, although a clinically important effect could not be ruled out, due to the wide 95% confidence intervals.
- Manual therapy showed no statistically significant beneficial short-term effects on pain compared with treatment as usual, based on pooled analysis of three RCTs and four additional RCTs (low strength of evidence).
- Manual therapy showed no consistent beneficial effects on short-term function, based on four RCTs (low strength of evidence).
- Insufficient evidence was found to assess medium-term effects of manual therapy on pain, function, and other outcomes, based on four RCTs.
- Manual therapy had a small beneficial effect on long-term pain of borderline significance when combined with exercise, compared with exercise alone, based on two studies that conducted 12-month follow-up of three-month interventions (low strength of evidence).
- Evidence was insufficient to assess effects on long-term function.

Findings

We identified nine RCTs that assessed the effects of manual therapy techniques, including massage and acupressure, (alone or combined with exercise programs). The details are described in the evidence table in Appendix C.

Short-term effects on pain. Seven RCTs reported on short-term effects of different manual therapies on pain: passive joint mobilization, self-manual therapy (with exercise), acupressure, and combined manipulation and passive mobilization with physical therapy/exercise.[67, 116-121] Because of the differences in interventions and outcome measures, only the results of three RCTs were pooled.

A 2011 RCT conducted in Malaysia by Azlin randomized 22 adults 40 years and older to passive joint mobilization plus their regular exercise or to exercise alone, two sessions per week for 4 weeks (RoB high).[116] Among the 13 completers, at 4 weeks, both groups experienced pain relief (improvement in VAS scores) at 4 weeks, and no difference was seen between groups (MD -2.99, 95% CI -21.54, 15.56).

A 2014 RCT conducted in the US by Perlman and colleagues randomized 125 individuals to one of five 8-week interventions, comprising 30- or 60-minute weekly or bi-weekly massages or a TAU group (RoB moderate).[121] At 8 weeks, participants who got two 30-minute massages per week (MD -16.30, 95% CI -30.17, -2.43) and those who received one or two 60-minute massages per week (MD -30, 95% CI -42.09, -17.91) (MD -21.40, 95% CI -33.42, -9.38) had significantly improved VAS pain scores compared with the TAU group but the 30-minute per week massage group did not (MD -4.40, 95% CI -18.27, 9.47). Participants who received one or two 60-minute massages per week (MD -21.60, 95% CI -33.47, -9.73; MD -22.10, 95% CI -33.89, -10.31) had significantly improved WOMAC pain scores compared with the TAU group but the 30-minute once or twice per week massage groups did not (MD -9.50, 95% CI -20.69, 1.69) (MD 3.60, 95% CI -8.70, 15.90).

A 2014 RCT conducted in Thailand by Cheawthamai randomized 43 women to a 12-week home-based self-manual therapy and exercise program or exercise alone (RoB moderate).[117] At 4 weeks, both groups showed improved KOOS pain scores but no significant difference was observed between the groups.

A 2012 pilot RCT conducted in the US by Zhang randomized 36 postmenopausal women to a 12-week self-administered acupressure program (with a training module) or to treatment as usual (RoB moderate).[119] At 6 weeks, no significant differences were seen in WOMAC pain scores between the two groups (MD -1.15, 95% CI -3.45, 1.15).

A 2014 RCT conducted in Spain by Godoy randomized 18 women to a 6-week intervention comprising either a combination of massage therapy and exercise or exercise alone (RoB low).[118] At 1-month followup, no differences were observed between groups in VAS pain scores (MD 3.10, 95% CI 0.76, 5.44).

A 2015 two-site pilot RCT conducted in South Africa and the US by Dwyer randomized 83 individuals to one of three 4-week interventions: manual and manipulative therapy (MMT) alone, rehabilitation (rehab, a physical therapist-directed exercise program) alone, and MMT plus rehab (RoB moderate).[120] At 6 weeks from baseline, participants in the MMT plus rehab group had decreases in WOMAC pain scores (less pain) that did not differ significantly from those of the group that received rehab alone (MD -26.90, 95% CI -68.88, 15.08) using a WOMAC scoring system with a maximum of 500 points).

A 2016 RCT conducted in New Zealand by Fitzgerald randomized 300 patients with knee OA to one of four interventions: 9 weeks exercise alone, 9 weeks exercise plus manual therapy delivered by a physical therapist, or the same two interventions with 8 booster sessions over the subsequent 10 months (Low RoB).[67] At 9 weeks, no differences were seen in pain scores between the exercise only group and the group that received the exercise plus manual therapy.

A random-effects meta-analysis of three of the trials[119-121] showed no significant effect of manual therapy (administered by a therapist or by patients themselves) on short-term WOMAC pain (n=137; SMD -0.57, 95% CI -1.60, 0.45) (Figure 16).

Figure 16. Forest plot for short-term effects of massage or acupressure on WOMAC pain score

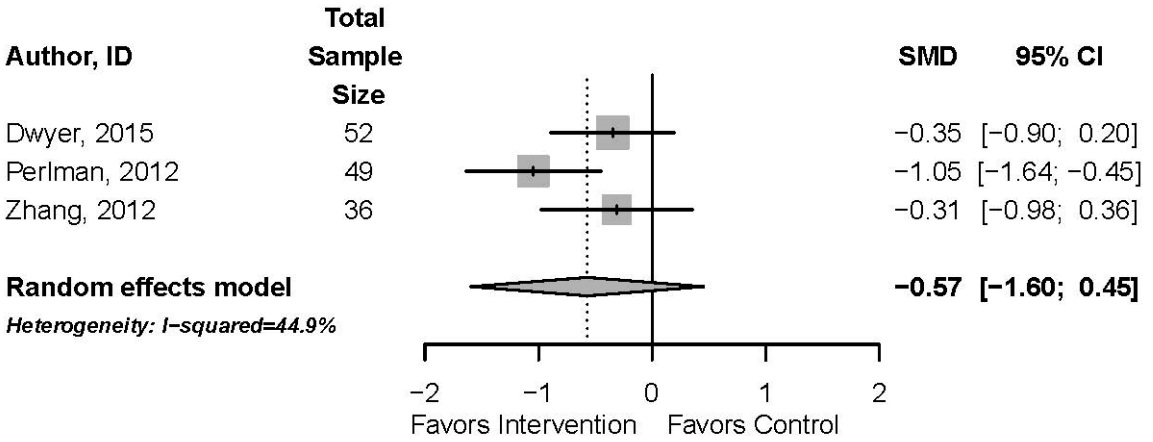


Figure notes: CI=confidence interval; SMD=standardized mean difference; WOMAC=Western Ontario and McMaster Arthritis Index

Short-term effects on function. At 6 weeks, both Zhang and Dwyer reported no significant between-group differences in WOMAC function scores at 6 weeks (MD -3.40, 95% CI -12.56, 5.76 and MD -32.80, 95% CI -191.40, 125.80, using a 1700-point tool, respectively).[119, 120]

At 8 weeks, Perlman reported significant improvements in WOMAC function compared with TAU in the groups who received one 30-minute massage per week (MD -11.40, 95% CI -20.90, -1.90) or one or two 60-minute massages per week (MD -14.60, 95% CI-24.50, -4.70) (MD -15.40, 95% CI -26.48, -4.32) but not in the group that received two 30-minute massages per week (MD-10.60, 95% CI -21.76, 0.56).

Short-term effects on other outcomes. Five RCTs reported short-term effects on other relevant outcomes.[67, 117-120]

Zhang reported no significant difference between treatment groups in WOMAC total scores (MD -5.51, 95% CI -16.97, 5.95).[119] Dwyer also reported no significant differences between groups in WOMAC total score (MD -63.20, 95% CI -273.72, 147.32).[120] Godoy reported no between-group differences in total WOMAC score (MD 21.42, 9.79, 33.05) or TUG (MD 3.94, 95% CI -4.01, 11.89).[118]

Perlman reported differences in total WOMAC scores between the groups who received massages for 30 minutes, twice a week (MD -12.10, 95% CI -23.31, -0.89) and 60 minutes, once a week (MD -17.70, 95% CI -28.02, -7.38) and treatment as usual but not those who received one 30-minute massage or two 60-minute massages per week.[121]

Godoy reported no between-group differences in TUG (MD 3.94, 95% CI -4.01, 11.89).[118]

Cheawthamai reported no significant between-group differences in the 6-minute walk test and the SF-36 physical functioning domain.[117]

Fitzgerald reported significant improvements in WOMAC total scores (MD −4.50, 95% CI −8.66, −0.34) and in TUG scores (MD −0.20, 95% CI −0.36, −0.04) at 9 weeks in the group that received both exercise and manual therapy compared with the group that received exercise alone.[67]

Medium-term effects on pain. A 2013 RCT conducted in the US by Atkins and Eichler randomized 40 adults (age 50 and over) with knee OA to 8 weeks of supervised self-massage and 4 weeks of unsupervised self-massage or to a waiting list control group (RoB unclear).[122] At the end of the intervention, a significant between-group difference was observed in WOMAC pain scores (MD -0.65, variance not calculable).

At 3-months' followup, the Godoy RCT found no differences between groups in VAS pain scores (MD 2.28, 95% CI 0.44, 4.12).[118] At 12 weeks, Zhang reported no between-group differences in WOMAC pain scores (MD -1.88. 95% CI -10.58, 6.82).[119] At 6 months, Perlman reported no differences in WOMAC pain between groups who received one or two massages per week and the TAU group.[121]

Medium-term effects on function. At 3 months, Zhang reported no between-group differences in WOMAC function scores (MD -1.88. 95% CI -10.58, 6.82).[119]At 6 months, Perlman reported no differences in WOMAC function scores between groups who received one or two massages per week and the TAU group.[121] At 3 months, Atkins reported a significant difference in WOMAC function scores (MD -0.80, variance not reported).[122]

Medium-term effects on other outcomes. At 3 months, Zhang reported no between-group differences in WOMAC stiffness or total scores.[119] Also at 3 months, Atkins reported significant between-group differences in WOMAC stiffness (MD -0.8, no variance reported) and total WOMAC (MD -0.7, no variance reported) scores.[122] At 6 months, Perlman reported no differences from TAU in WOMAC total among any of the massage groups.[121]

Godoy reported no differences in TUG at 3 months (MD 14.04, 95% CI 4.71, 23.37).[118]

Long-term effects on pain. A 2015 pilot RCT conducted in New Zealand by Abbott and colleagues randomized 75 participants to one of four interventions: 12 sessions of exercise alone (9 weeks), 8 sessions of exercise (9 weeks) plus 4 additional sessions over the ensuing 8 months, exercise plus 12 sessions of manual therapy, or exercise plus extra sessions plus manual therapy (RoB moderate).[65] At one year, compared with the exercise-only group, the group that received exercise plus manual therapy had significantly improved pain intensity scores compared with the group that received exercise alone (MD -2.30, 95% CI -4.07, -0.53).

At 12 months, the 2016 Fitzgerald RCT, conducted by the same research team that conducted the 2015 pilot RCT by Abbott, found a small improvement in pain of borderline significance among the participants who received 2 months of both exercise and manual therapy compared with exercise alone (MD −0.20, 95% CI −0.36, −0.04) as well as among those who received exercise plus booster sessions plus manual therapy (MD −0.70, 95% CI −0.90, −0.50).

Long-term effects on other outcomes. At 12 months, the Fitzgerald RCT found no difference in WOMAC total (the primary outcome measure) between the participants who received 2 months of both exercise and manual therapy compared with exercise alone as well as between those who received exercise plus booster sessions plus manual therapy and those who received only exercise and booster sessions. However, manual therapy significantly improved TUG scores in the exercise group (MD −0.30, 95% CI −0.46, −0.14) compared with exercise alone.

Weight Loss

Key Points

- Weight loss with or without exercise has a beneficial effect on medium-term pain and function and on long-term pain but inconsistent effects across studies on long-term function and quality of life.
    - Evidence was insufficient to assess short-term effects of dieting, with or without exercise on pain and function,.

- Weight loss had a significant beneficial effect on medium-term pain, based on two RCTs and four single-arm trials. One single-arm trial assessed and reported a dose-response effect between weight and outcomes of interest (moderate-level evidence).
- Weight loss had a significant beneficial effect on medium-term function, based on two RCTs and three single-arm trials (low strength of evidence).
- Weight loss had a significant long-term beneficial effect on pain based on three RCTs and one single-arm trial (low level of evidence) but inconsistent effects on function and quality of life, based on two RCTs (low strength of evidence).

Findings

We identified five RCTs[123-127] and five single-arm trials [68, 128-132] reported in six publications that reported on the effects of weight loss trials among individuals with knee OA on outcomes of interest.[123-127] The details are described in the evidence table in Appendix C.

Randomized Controlled Trials

Short-term effects on pain. One trial reported on short-term effects of a weight-loss trial on outcomes of interest. A 2008 RCT conducted in Tunisia by Ghroubi and coworkers randomized 45 obese adults (BMI>35 or between 30 and 35 with one cardiovascular risk factor) and radiographic OA of the knee to an aerobic and strength training program (exercise) alone, diet plus exercise, diet alone, or a no diet/no exercise control (RoB unclear).[123] At 8 weeks, the diet plus exercise group had lost significantly more weight than the other groups, followed by the diet only group, and then the exercise only group (the control group lost no weight). The diet + exercise group showed a significant between-group difference in VAS pain (1-10cm, MD -4.56, 95% CI -5.82, -3.30) compared with the control, as did the diet alone group (MD -2.10, 95% CI -3.32, -0.88); the exercise only group also showed improvement in pain compared with the control (MD -2.90, 95% CI -4.52, -1.28).

Short-term effects on function. The RCT by Ghroubi assessed the effects of diet with or without exercise on three measures of function.[123] All three active treatment groups showed comparable improvements in WOMAC function scores (exercise only: MD, -3.09 95% CI -4.46, -1.72 ; exercise+diet: MD -4.01, 95% CI -5.56, -2.46; diet only: MD -2.34, 95% CI -3.71, -0.97) and Lequesne scores (exercise only: MD -2.41, 95% CI -3,52, -1.30; exercise+diet: MD -3.73, 95% CI -4.65,-2.81; diet only: MD -2.23, 95% CI -3.30, -1.16) compared with the control.

The proportion of participants who achieved a significant improvement in WOMAC function was greater in each of the active treatment groups compared with the control group (exercise only RR 0.23, 95% CI 0.02, 2.23; exercise+diet: RR 0.16, 95% CI 0.02, 1.39; diet only: RR 0.33, 95% CI 0.03, 3.43).

Short-term effects on other outcomes. The Ghroubi RCT found that exercise alone (MD -39.00, 95% CI -46.47, -31.53) and exercise+diet (MD -53.00, 95% CI -59.33, -46.67) significantly improved 6-minute walk distances but diet alone (MD 2.00, 95% CI -6.51, 10.51) did not.[123]

Medium-term effects on pain. Two RCTs assessed the effects of weight loss on medium-term pain.[124, 127]

A 2006 U.S. RCT, the Physical Activity, Inflammation, and Body Composition Trial, randomized 87 obese adults over 60 years to a 6-month intensive weight loss group or a weight maintenance group; the weight loss goal was a 10% body weight loss (RoB moderate).[124] At 6 months, the weight loss group had lost an average of 8.3±0.8 kg and decreased an average of 8.1±0.7 BMI units (compared with 0.1±0.7 kg and 0.3±0.9 BMI units in the control group).

WOMAC pain scores showed a significant between-group difference in favor of the weight loss group (MD -2.00, 95% CI -3.25, -0.75).

The OA Life Study was a 2012 U.S. RCT that randomized 232 obese adults with knee OA to receive standard care, a pain coping skills training (PCST) program, a behavioral weight management (BWM) program alone, or both interventions (RoB moderate).[127] Both the BWM and BWM+PCST groups had significant weight losses compared with the standard care group; only the BWM+PCST group had a significant decrease in BMI compared with standard care (MD -1.80, 95% CI -2.44, -1.16). No difference was observed in WOMAC pain between the BWM group and the standard care group (MD −2.50, 95% CI −7.67, 2.67), but a significant between-group difference was seen between BWM+PCST and the standard care group (MD −10.80, 95% CI −15.77, −5.83).

Medium-term effects on function. Two RCTs assessed the effects of weight loss on WOMAC function.

The Physical Activity, Inflammation, and Body Composition Trial found a significant between- group difference in WOMAC function between the weight loss and weight maintenance groups, favoring the weight loss group.[124]

The OA Life Study observed a significant difference in WOMAC function between the PCST+BWM group and the standard care group (MD -12.40, 95% CI -17.29, -7.5) but no significant difference between the BWM-only group (which achieved lower weight loss than the PCST+BWM group) and the standard care group (MD-1.50, 95% CI -6.46, 3.46).[127]

Medium-term effects on other outcomes. The Intensive Diet and Exercise for Arthritis (IDEA) Trial is a 2013 U.S. RCT that randomized 454 overweight and obese adults (BMI 27-41) with knee OA to an intensive diet and exercise-based weight loss program, diet alone, or exercise alone (exercise was considered part of standard care) (RoB moderate).[125] At 6 months, neither diet alone nor diet plus exercise affected scores for the 6-minute walk or the physical domain of the SF-36.

The 2006 Physical Activity, Inflammation, and Body Composition Trial found a significant between-group difference in the distance walked in the 6-minute walk test (MD -51.00, 95% CI -96.03, -5.97) and in WOMAC total scores (scale not reported, MD -10.70, 95% CI -17.01, -4.39).[124]

Long-term effects on pain. A 2011 publication reported on a 2005 RCT conducted in Denmark by Bliddall and colleagues that had randomized 89 knee OA patients to an intensive weight loss program (6 weeks of an intensive low energy diet [LED], along with group counseling) or a control group (moderate calorie restriction and education only); at 1-year, the researchers followed up on the 80 retained patients (RoB moderate).[126] The LED group had lost significantly more weight than the control group (kg, MD -7.30, 95% CI -9.52, -5.08), and was experiencing significantly less pain than the control group, as assessed on the WOMAC scale (0-100 points, MD -7.20, 95% CI -13.30, -1.10). The primary endpoint, WOMAC total score, is reported below.

In the IDEA Trial, at 18 months, weight loss was slightly but significantly greater in the diet+exercise group than in the diet-only group, compared with the exercise-only group (MD -8.10, 95% CI -11.92, -4.28 versus MD -6.00, 95% CI -9.75, -2.25). Primary outcomes were knee-joint loading and interleukin-6 levels. The diet+exercise group experienced a nonsignificantly greater improvement in WOMAC pain measures than the exercise-only group (20 pts total, MD -0.70, 95% CI -1.41, 0.01), and the diet only group showed no difference in WOMAC pain measures.[125]

At 18 months, the OA Life Study showed that patients in the PCST+BWM group continued to experience less pain than the standard care group (MD −14.00, 95% CI −24.77, −3.23, although all groups had regained some of the lost weight (no statistics reported).[127]

Long-term effects on function. Bliddall found no significant between-group differences in WOMAC function in their diet study.[126]

The IDEA trial reported a significant between-group difference in WOMAC function for the diet+exercise group compared with the exercise only group (MD -3.40, 95% CI -6.02, -0.78); the diet-only group did not differ from the exercise-only group.[125]

Long-term effects on other outcomes. Bliddall found no significant between-group differences in WOMAC total in their diet study.[126]

The IDEA trial reported significant between-group differences in 6-minute walk test performance (meters walked, MD -12.00, 95% CI -33.93, 9.93) and the SF-36 physical domain scores (0-100 points, MD -2.70, 95% CI -4.89, -0.51) for the diet+exercise group compared with the exercise-only group but no significant differences between the diet-only group and the exercise-only group.[125]

Single Arm Trials

We identified five single-arm trials reported in six publications[68, 128-132] that assessed the effects of weight loss on outcomes of interest.

Short-term effects on pain. A 2015 single-arm trial conducted in Australia by Claes and colleagues followed 203 individuals with knee OA in a 12-week hospital-based weight loss program to assess the effects of a weight loss program on the primary outcomes of weight loss and decrease in waist circumference and secondary outcomes related to knee pain and function.[130] Among 127 completers, percentage weight loss and decrease in BMI were significant at 12 weeks. This group demonstrated a significant improvement in KOOS pain scores (MD 5, 95% CI 2.0, 97.9).

Short-term effects on other outcomes. One trial was identified that reported on the association of weight loss with other short-term outcomes of interest.[130]

The 2015 trial by Claes reported a significant improvement in the timed up and go (seconds, MD−1.4, 95% CI−1.1 to −1.7) and the 6-minute walk test (meters, MD 36.7, 95% CI 27.2, 46.2)) from baseline to 12 weeks.[130]

Medium-term effects on pain. Four studies assessed the association between medium-term weight loss and pain.[68, 128, 130, 131]

A 2014 study conducted in Denmark by Bartels and colleagues followed a cohort of 192 participants (age over 50, BMI 30 or over) in a 16-week weight loss program, part of the CAROT study (Influence of weight loss or exercise on CARtilage in Obese knee osteoarthriTis patients) who experienced a significant weight loss (MD 14, 95% CI 13.3, 14.7).[68] Weight loss was significantly associated with improvement in KOOS pain scores (MD 10.7, 95% CI 8.5, 12.9).

A 2015 study conducted in Australia by Messier, Bennell, and colleagues (Atukorala et al., 2015) enrolled over 3,000 overweight individuals with knee OA in an 18-week weight loss program and assessed the association between percent body weight loss and change in knee pain in 1,383 completers (94 of whom had lost more than 2.5% of their original body weight).[128] At 18 weeks, quintiles of weight loss (as % of baseline body weight) showed a significant dose-response relationship with KOOS pain scores (e.g., >10% weight loss [n=431]: MD 16.7, 95% CI 15.2, 18.2) compared to <2.5% weight loss [n=79] MD 6.1, 95% CI 3.2, 9.0; full data reported in Appendix C). Quintiles showed no significant differences in age or sex.

The 2015 study by Claes reported that among 76 participants who were retained at 26 weeks, weight loss was 2.1 ± 4.0 kg and improvement in VAS pain (0-10cm, −0.9 ± 2.0) and changes in KOOS pain at 26 weeks remained significant (MD 5.6, 95% CI 1.6, 9.6).[130]

A 2011 single-arm study conducted in France by Richette prospectively assessed the effects of large-scale weight loss among 44 bariatric surgery patients with moderate to severe OA of the knee on pain after 6 months (RoB not determined).[131] At 6 months, patients experienced a significant improvement in BMI (10.3, 95% CI 7.4, 13.2), and VAS (0-100 scale, MD 25.5, 95% CI 15.5, 35.5) and WOMAC (no scale, MD 93.2, 95% CI 47.1, 139.3) pain scores were significantly improved compared with baseline.

Medium-term effects on function. Three studies[68, 128, 131] assessed the association of weight loss with function.

Richette demonstrated significant improvements in WOMAC function scores with weight loss at 6 months (MD 371.3, 95% CI 219.6, 523.0).[131]

The 2014 study conducted by Bartels and colleagues reported a significant improvement in KOOS function associated with weight loss (MD 12.1, 95% CI 10.0, 14.2).[68]

The study by Atukorala found a significant dose-response relationship between percent weight loss and KOOS function scores (>10% loss: MD 17.4, 95% CI 15.9, 18.9 compared with <2.5% loss: MD 7.8, 95% CI 4.8, 10.8).[128] Achievement of a MCID in KOOS function was associated with a weight loss of 7.7 percent or more (95% CI 5.2, 13.3).

Medium-term effects on other outcomes. We identified three single-arm trials that assessed medium-term effects on other outcomes of interest among weight loss patients with OA.

At 6 months, patients in the bariatric surgery trial by Richette showed significant improvements in WOMAC stiffness scores (MD 31.8, 95% CI 11.7, 51.9).[131]

The 2015 trial by Claes reported a significant improvement in the timed up and go (seconds, MD 2, 95% CI 1.4, 2.6) and the 6-minute walk test (meters, MD 44.0, 95% CI 31.5, 56.5) from baseline to 26 weeks.[130]

The 2015 study by Atukorala also identified a significant dose-response association of percent body weight lost and the SF-12 physical domain (<2.5%: mean 3.16 [SD 8.24]; 2.5-5%: 4.07 [8.02]; 5.1-7.5%: 6.73 [7.83]; 7.6-10%: 6.65 [8.17]; > 10%: 8.60 [8.18], p=0.000).[129]

Long-term effects on pain. We identified one single-arm trial that assessed long-term effects on pain.

A 2015 U.S. study by Stefanik and colleagues, the Osteoarthritis Before and after Bariatric Surgery study, is assessing the effect of large-scale weight loss on knee OA outcomes among individuals with BMI 35 or higher (RoB not assessed).[132]At 1 year, among 23 individuals who have completed the study so far, VAS (0-100mm, MD 27.8) and WOMAC (0-20 points, MD 5.1) pain scores have improved.

Home-Based and Self-Management Interventions

Key Points

- A home-based exercise program and a self-management plus exercise program showed significant beneficial short-term effects on pain, based on two RCTs (low strength of evidence).
- Evidence was insufficient to assess the effects of home-based and self-management programs on short-term function but self-management programs had significant

beneficial effects on medium-term function compared with control conditions (low strength of evidence.
- Self-management and PCST plus strength training showed beneficial but inconsistent medium-term effects on pain, based on three RCTs (low strength of evidence).
- Evidence was insufficient to assess the medium-term effects of self-management programs on quality of life.
- Evidence was insufficient to assess the long-term effects of self-management on pain or function.

Findings

Most RCTs included in the current report expected participants to perform exercises at home, but none of these trials assessed the effects of compliance or adherence with the home exercise assignments. We identified five RCTs that reported on the effects of home-based or self-management interventions (described as self-management or coping skills training) among individuals with knee OA on outcomes of interest.[42, 46, 53, 127, 133] Three of these studies have been described in previous sections of the report, and the details are described in the evidence table in Appendix C.

Randomized Controlled Trials

Short-term effects on pain. Two RCTs that met inclusion criteria assessed short-term effects of self-management or home-based interventions on pain.[46, 133]

A 2012 RCT conducted in the US by Rogers and coworkers randomized 44 adults age 50 and over to one of four 2-month home-based interventions: kinesthesia, balance, and agility (KBA) training alone, resistance training (RT) alone, a combination of KBA and RT, and a control group that was told to apply a lotion to the affected areas (RoB moderate).[46] At 2 months, WOMAC pain scores improved significantly for all groups compared with the control group (Strength training alone: MD -3.75, 95% CI -6.39, -1.11; agility training alone: MD -3.13, 95% CI -5.86, -0.40; strength+agility training: MD -3.00, 95% CI -5,45, -0.55), with no significant differences between any of the groups.

A 2012 RCT conducted in Australia by Coleman and colleagues, the OAK Self Management Program (OAK) study, randomized 146 adults to a 6-week self-management intervention tailored to knee OA patients (based on the Stanford Arthritis Self-management Program) or to a waiting list control group (RoB low).[133] At 2 months, a significant between-group difference was seen in WOMAC pain scores (MD -1.50, 95% CI -2.33, -0.67). VAS pain decreased significantly over the same time period (0-10cm MD 2.54, 95% CI 1.66, 3.41), and the likelihood of achieving a minimum clinically important improvement (MCII) was significantly greater in the SM group (RR 0.20, 95% CI 0.08, 0.49).

Short-term effects on function. Two RCTs that met inclusion criteria assessed short-term effects of self-management or home-based interventions on function.[46, 133]

The Rogers trial reported significant between-group differences in WOMAC function at 2 months for the combined strength+agility training group (MD -11.98, 95% CI -19.15, -4.81) and the strength training group (MD -9.62, 95% CI -19.04, -0.20) compared with the controls but not the group that performed agility exercises alone.[46]

The 2012 OAK study found a significant between-group difference in WOMAC function scores at 2 months (MD -5.30, 95% CI -7.24, -3.36).[133] In addition the proportion achieving a MCII was significantly different (RR 0.24, 99% CI 0.11, 0.51).

Short-term effects on other outcomes. Two RCTs that met inclusion criteria assessed short-term effects of self-management or home-based interventions on other outcomes.[46, 133]

The Rogers trial of home-based interventions reported significant between-group differences in WOMAC total at 2 months for the combined strength+agility training group (MD -15.26, 95% CI -25.16, -5.36) and the strength training group (MD -13.62, 95% CI -26.37, -0.87) compared with the controls but not the group that performed agility exercises alone.[46]

The 2012 OAK self-management study found significant between-group differences in WOMAC total scores at 2 months (MD -7.20, 95% CI -9.97, -4.43). The study also found significant between-group differences in SF-36 physical domain scores at 2 months (MD -5.60, 95% CI -9.48, -1.72) and a significant increase in the likelihood of achieving a MCII (RR 0.57, 95% CI 0.38, 0.84). Significant between-group differences were seen in 2-month TUG scores (MD -1.00, 95% CI -1.55, -0.45) and in the likelihood of achieving a MCII in TUG (RR 0.32, 95% CI 0.20, 0.52).[133]

Medium-term effects on pain. Three RCTs assessed medium-term effects of home-based or self-management interventions on pain.[53, 127, 133]

A 2016 double-blind (participants and assessors) RCT conducted at two sites in Australia by Bennell and colleagues assessed the effect of strength training combined with pain coping skills training (PCST) compared with PCST or strength training exercises (the control) alone (RoB low).[53] This study randomized 222 individuals with moderate to severe knee OA to one of three 3-month treatment programs and followed them for 12 months. Overall pain was assessed on a 100mm VAS scale with a MCID set at 18mm. Comparisons used a model that took into account the physical therapist training, baseline scores, site, and sex. At 3 months, no significant differences were observed in overall pain in the group that received strength training+PCST or the group that received PCST alone compared with the group that received strength training alone. A significant between-group difference was observed in VAS walking pain, favoring the group that received strength training+PCST over that of strength training alone (MD -8.20, 95% CI -15.32, -1.08). Using WOMAC pain as the outcome, a nonsignificant difference was seen in the strength training+PCST group compared with strength alone and no difference was seen comparing PCST alone with strength training.

The OA Life Study was a 2012 U.S. RCT that randomized 232 obese adults with knee OA to receive standard care, a pain coping skills training (PCST) program, a behavioral weight management (BWM) program alone, or both interventions (RoB moderate).[127] Both the BWM and BWM+PCST groups had significant weight losses compared with the standard care group; only the BWM+PCST group had a significant decrease in BMI compared with standard care (MD -1.80, 95% CI -2.44, -1.16). No difference was observed in WOMAC pain between the BWM group and the standard care group (MD -2.50, 95% CI -7.67, 2.67), but a significant between-group difference was seen between BWM+PCST and the standard care group (MD -10.80, 95% CI -15.77, -5.83).

The 2012 OAK self-management study found no remaining between-group differences in WOMAC pain at 6 months.[133]

Medium-term effects on function. Four RCTs assessed medium-term effects of home-based or self-management interventions on function.[42, 53, 127, 133]

The Bennell trial that compared strength+PCST training with each one alone observed a significant between-group difference in WOMAC function at 3 months, favoring the strength+PCST group over strength training alone (0-68 points, MD -3.80, 95% CI -7.06, -0.54).[53]

The 2012 OA Life Study observed a significant between-group difference in WOMAC function between the BWM+PCST group and the standard care group (0-100 points, MD-12.40, 95% CI -17.29, -7.51) but no other between-group differences.[127]

At 6 months, the 2012 OAK self-management study found a continuing between-group difference in WOMAC function (MD-3.50, 95% CI -6.14, -0.86) and an increase in the likelihood of achieving a MCII in function compared with the control group (RR 0.56, 95% CI 0.33, 0.95).[133]

The 2011 STAR feasibility study developed and tested self-efficacy strategies to promote fitness walking in an individually delivered home-based program for overweight and obese older adults with knee OA.[42] At the end of the 6-month program, no significant between-group differences were seen in WOMAC function or in performance on the 6-minute walk test compared with a usual care control group.

Medium-term effects on other outcomes. Two RCTs assessed medium-term effects of self-management or home interventions on other outcomes of interest.[53, 133]

The Bennell trial, which compared strength+PCST training with each one alone observed no between-group differences in TUG or in quality of life at 3 months.[53]

At 6 months, the 2012 OAK self-management study found a continuing between-group difference in WOMAC total scores (MD -4.10, 95% CI -7.43, -0.77). The study also found significant persistent between-group differences in SF-36 physical domain scores at 6 months (MD -5.70, 95% CI -10.97, -0.43) and a significant increase in the likelihood of achieving a MCII (RR 0.73, 95% CI 0.52, 1.02). Significant between-group differences persisted at 6 months in TUG scores (MD -1.00, 95% CI -1.55, -0.45) and in the likelihood of achieving a MCII in TUG (RR 0.68, 95% CI 0.47, 0.99).[133]

Long-term effects on pain. At 1 year, the Bennell trial, which compared strength+PCST training with each one alone, observed no between-group differences in VAS pain or WOMAC pain.[53]

Long-term effects on function. The Bennell trial, which compared strength+PCST training with each one alone, observed no between-group differences in WOMAC function at 1 year.[53]

The 2011 STAR feasibility test found no significant followup effects of the aerobic walking intervention at 12 months from baseline.[42]

Long-term effects on other outcomes. At 1 year, the Bennell RCT identified a significant between-group difference in quality of life (Australian Quol-6D) between the strength+PCST and the strength-only group (range -0.04-1 MD -0.06, 95% CI -0.11, -0.01),[53] but no differences in the TUG.

Key Question 2a: What harms are associated with each intervention in patients with primary or secondary OA of the knee?

Key Question 2b: How do the harms associated with each intervention differ by the following population or study characteristics: sex, disease subtype (lateral tibiofemoral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

Key Points

- Of 57 studies that described some assessment of adverse events (AEs), eighteen studies reported on serious adverse events (SAEs). Most reported only whether any SAEs were identified. SAEs were extremely rarely reported and not limited to active treatment groups. AEs are shown by study in Appendix H.
- No studies assessed differences in adverse events by characteristics of subpopulation.

Detailed Synthesis

Adverse events (AEs) were considered in 57 of the original studies included in the report, 18 of which made reference to SAEs. A large proportion of these studies declared that no AEs or no SAEs were reported. All AEs are shown in Appendix H by study, type, and number and percent per study arm. In this section, we highlight differences in AEs across study arms of interest. No differences in AEs were reported by any patient characteristics.

The quality of AE reporting was assessed using the McHarms tool. Findings are shown in Appendix F and described in the Discussion section.

Platelet-rich plasma (PRP). Of two studies on PRP that reported on AEs, one reported no serious AEs (SAEs),[25] and the other reported a significant increase in pain and stiffness with single injections, which doubled with two injections.[23]

Glucosamine and/or chondroitin. The GAIT trial reported on a large number of AEs, but almost none were observed across study arms. SAEs were rare and as likely to occur in the celecoxib and placebo controls as in glucosamine or chondroitin treatment groups. Notably, withdrawal due to AEs was slightly but probably not significantly higher for chondroitin alone than for any of the other interventions.[134] A 2-year trial of chondroitin sulfate compared with placebo found no difference in gastrointestinal AEs or withdrawal due to AEs.[37] The LEGS trial assessed withdrawals due to blood glucose issues and found no difference from placebo.[31] A 2016 study of chondroitin sulfate supplementation reported no difference between chondroitin and placebo in the risk for serious AEs or any AEs. The number of AEs related to treatment and the number that resulted in discontinuation were greater in the chondroitin group than in the placebo group but the article did not describe the specific AEs.[32]

Physical interventions. No AEs of note were reported among studies of strength, aerobic, agility, or other physical training interventions. A study of agility interventions (gait training) reported no AEs associated with either the active intervention or the control.[60] A study that

compared Tai chi to conventional physical therapy reported no serious AEs associated with either intervention.[70]

Mud baths were associated with mild hypotension among 5.66 percent of participants compared with no instances among sham controls.[75]

Braces, orthotics, and custom shoes. Among three RCTs that reported on AEs in studies of orthoses (lateral insoles) compared with neutral or no insoles, one reported significantly greater back pain, foot pain, and difficulty with shoe fit, but less knee pain among the lateral insole users.[109]

TENS, NMES, PEMF, and WBV. No differences were seen in AEs between active and control groups with the exception of one case (among 19 participants) of slight low back pain with WBV.[81, 86, 87, 92, 95]

Weight loss with or without exercise. One study of weight loss that tracked a large number of nonSAEs found an increase in minor GI AEs among those in the diet group.[62]

Pain Coping Skills Training (PCST). One study that compared a large number of categories of AEs among participants randomized to a PCST and exercise intervention with those among a group who received only exercise or only PCST found that PCST plus exercise was associated with a lower number of numerous types of AEs than the group that received only exercise.[53]

Discussion

Summary of Key Findings and Strength of Evidence

The key findings for each intervention appear in the Results section. Table 2 summarizes the findings, conclusions, and strength of evidence ratings that are reported in full in Appendix E.

In general, for the outcomes of interest, findings were insufficient to draw conclusions, or conclusions were supported by low levels of evidence. No conclusions were supported by a high level of evidence. This section highlights findings and conclusions for which we found moderate or low strength of evidence (SoE).

Cell-Based Therapies

Randomized controlled trials (RCTs) that met inclusion criteria were identified only for platelet rich plasma (PRP). Although we identified a low strength of evidence for a significant effect of PRP (compared with saline injections) on medium-term pain and quality of life, based on four RCTs, studies were small and of moderate to high risk of bias (RoB).

Glucosamine Chondroitin, Glucosamine, or Chondroitin

No studies were identified that assessed short-term outcomes of dietary supplementation with glucosamine, chondroitin, or the combination. Glucosamine combined with chondroitin showed a significant beneficial effect on medium-term pain and function. This conclusion is based only on a low SoE, because of the small number of newer (albeit large) trials, lack of consistent effects across studies, and lack of pooling. Moderate levels of evidence from three large trials support no long-term effects of glucosamine plus chondroitin or chondroitin sulfate alone on pain, function, and other outcomes (low strength of evidence for effects of chondroitin on function). Glucosamine alone showed no benefits for pain or function, although a post hoc analysis of two large RCTs showed a decrease in the long-term risk for total knee replacement (TKR).

Physical Interventions

Low-level evidence supports a lack of significant short-term benefits of strength/resistance training programs on pain or function (based on 5 pooled RCTs, each). The strength of evidence was low because of inconsistency across the trials (one outlier study in each) and study quality. A significant short-term effect of strength training was seen on total Western Ontario and McMaster Universities Arthritis Index (WOMAC) across three RCTs, but these studies could not be pooled. The disparity between effects on WOMAC pain and function and on total WOMAC scores is attributable to the one outlier study, which reported WOMAC pain and function scores but not WOMAC total scores. Because the goal of strength or resistance training for osteoarthritis (OA) of the knee is to strengthen the quadriceps muscles, which help support the knees, a medium- or long-term effect would be expected, but the evidence is insufficient to address long-term effects, primarily because of the small number of such studies.

Agility training programs (such as gait retraining) showed a beneficial effect on short term pain, no effect on short-term function or medium -term outcomes, but a significant benefit on long-term pain and function. Aerobic exercise programs showed a lack of long-term effect on knee function; evidence was insufficient to assess its shorter-term effects. General exercise programs, which are probably the most similar in design to the multicomponent treatment programs used by

physical therapists, showed beneficial effects on medium-term pain and function and on long-term pain; evidence was insufficient to assess effects on long-term function.

Tai chi showed beneficial effects on short-term pain and function in three RCTs (including one very recent very low RoB study) and beneficial effects on medium-term pain and function in two RCTs. Evidence was insufficient to assess long-term benefit.

Low-level evidence from three pooled studies and four studies that could not be pooled suggests a nonsignificant beneficial short-term effect of manual therapy (massage, acupressure, self-massage) on pain, but no effect on function. Two RCTs reported significant long-term benefit on pain. However, too few studies assessed similar enough interventions to consider conclusions about manual therapies to be truly meaningful.

Therapeutic ultrasound had insufficient evidence on which to base conclusions regarding benefit. Pooled analysis of three small RCTs showed a nonstatistically significant benefit of PEMF for short-term pain.

Moderate-level evidence from three pooled RCTs supports a statistically significant short-term beneficial effect of TENS on pain compared with a sham control, but the standardized mean difference (SMD) did not reach the prespecified minimum clinically important difference (MCID). No benefit of TENS was observed on short-term function or on any medium-term effects. No RCTs were identified that assessed effects of TENS on long-term outcomes.

Pooled analysis of four RCTs on whole body vibration (WBV) showed a statistically significant beneficial effect on medium-term function that did not meet the MCID (low strength of evidence [SoE]). No significant benefit of WBV was found for short- or medium-term pain, and no studies assessed long-term effects.

Orthoses

No consistent beneficial effects were found for shoe inserts on short- or medium-term pain or function, possibly due to the heterogeneity across intervention types. Insufficient evidence was found for effects of knee braces, custom shoes, and cane use.

Weight Loss

For this outcome, we included RCTs and single-arm trials. Moderate-level evidence (based on 2 RCTs and four single-arm trials) supports benefits of weight loss (with or without exercise) on medium-term pain and function, and other outcomes, including timed walking. Low-level evidence also supports a benefit of weight loss on long-term pain but evidence was insufficient to assess other potential long-term benefits. Too few studies were identified to assess the contribution of exercise.

Self-Management and Home-Based Programs

For this review, we assessed the effects of programs aimed at teaching self-management together with programs that promoted home-base exercise, based on the idea that both types of programs share similar goals of patients managing their own care, even though the programs have differences. A beneficial effect of self-management and home-based exercise programs on short-term pain and WOMAC total scores and on medium-term pain and function are supported by low-level evidence.

Adverse Events

Low-to moderate-level evidence supports a lack of systematic nonserious AEs and SAEs among interventions. Assessment and reporting were inconsistent.

Summary of Findings in Relationship to What Is Already Known

Platelet-rich plasma. The current review identified beneficial short-term effects of PRP. Several 2015 SRs reviewed the effects of PRP, however all prior reviews included studies comparing PRP to hyaluronic acid or corticosteroid injections. We included only studies that compared PRP to saline injections to control for any placebo effect. Thus, we identified too few studies to pool.

Glucosamine with or without chondroitin. The 2007 SR found no significant benefit for glucosamine, glucosamine plus chondroitin, or chondroitin alone, compared with placebo, based on the large (n=1,583) GAIT trial.

New RCTs identified for this review provided conflicting evidence for effects of supplemental glucosamine, chondroitin, or the combination. A large noninferiority trial found comparable short- and medium-term effects for glucosamine plus chondroitin compared with NSAIDs, but no long-term effects of either. This trial did not include a placebo control. The 2008 post hoc analysis conducted by the authors of the GAIT trial found that when participants were stratified by baseline pain, those with moderate to severe pain demonstrated a trend toward improvement from glucosamine plus chondroitin (proportion experiencing 20 percent or greater improvement in pain).[134] The effect was moderated by the large placebo response. No new trials assessed short- or medium-term effects of glucosamine sulfate alone; three RCTs found no consistent long-term effects on outcomes of interest. Chondroitin showed evidence of medium-term effects but no long-term effects, in three new trials and a long-term followup of the GAIT trial. The analysis also found that the effect of chondroitin on swelling was seen predominantly in those with less-advanced disease.

Strength and resistance training. The 2012 SR found low-level evidence that "strengthening exercise" decreased pain and improved several other outcomes among individuals with OA of the knee, but no evidence for improvement in function was supported. That review did not describe their criteria for categorizing an intervention as a strengthening exercise intervention; therefore we have not attempted to pool studies identified for this report with theirs.

The current review strengthens the findings of the 2012 review on beneficial effects of strength and resistance training on pain. We identified evidence for a significant beneficial effect on total WOMAC scores and a nonstatistically significant beneficial effect on short-term pain and function based on pooled analysis of five RCTs. An ongoing RCT, the Strength Training for Arthritis Trial (START, ClinicalTrials.gov NCT01489462) is testing whether higher intensity, longer duration strength training can reduce long-term pain and OA progression by further increasing quadriceps strength and offloading stress on the knee joint.[135]

Agility training. The current report identified low-strength evidence from six RCTs that strengthened the findings of the 2012 report on beneficial effects of agility training on long-term pain,[19] as well as providing evidence on short-term benefits for pain (low strength of evidence).

Tai chi. The current report identified low-strength evidence supporting a beneficial effect of Tai chi on short-and medium-term pain and function, augmenting the findings of the 2012 report.

Yoga. The current report did not identify sufficient evidence to augment the findings of the 2012 report on aerobic exercise or yoga. A 2016 SR on the effects of yoga on OA of the knee found a significant short-term effect on pain; this review included six studies, some with very short follow-up times.[136]

Manual therapy. For the current review, we found low-strength evidence for a lack of beneficial effect of manual therapy on short-term pain, based on three pooled RCTs, but no consistent effects on medium-term pain, function, or other outcomes, likely due to wide variation among the interventions, which included both physical therapist-applied manual therapy, therapeutic massage, and self-administered acupressure. The 2012 SR reported a low strength of evidence for an effect of massage on function based on two pooled studies (6-13 weeks) and reported improvements in disability and other outcomes based on three unpooled studies.

WBV. The current review identified a significant beneficial effect of WBV on medium-term function but not on medium-term pain, based on pooled analysis of three RCTs (low-strength evidence). Insufficient evidence was found for short- and long-term effects. The 2012 SR did not consider WBV as an intervention, and no other recent high-quality SRs assessed the effects of WBV on pain or function.

TENS and NMES. The current review found a beneficial short-term effect of TENS on pain, based on a MA of three RCTs (moderate-level evidence), but no consistent effects of TENS on function and no medium- or long-term effects. The review found insufficient evidence to draw conclusions regarding the effects of NMES on pain or function; further, strength, which is considered the primary outcome for NMES, was not included as an outcome of interest in the current study, and only two of the four studies that assessed NMES assessed strength.

The 2012 SR identified a beneficial effect of electrical stimulation, (including TENS and NMES) on short-term pain, based on meta-analysis of seven RCTs, but no other significant effects of electrical stimulation.[19]

Orthoses (knee braces, shoe inserts, custom shoes, and cane use. The 2012 SR identified low-level evidence for an effect of foot orthoses on function.[19] That review did not identify studies on cane use, knee braces, or shoes.

The current review found no beneficial effects of shoe inserts on pain or function in pooled analyses. A 2015 Cochrane update review assessed the efficacy of orthoses (including one type of shoe, a custom variable-stiffness shoe) and knee braces.[137] That review included only one RCT that was published since the 2012 SR (included in the current review) and, in agreement with the current review, concluded that braces and orthoses had no consistent effects on pain or function.

Other physical interventions. The current report did not identify evidence of sufficient strength to augment or contradict the findings of the 2012 SR on therapeutic ultrasound, pulsed electromagnetic field therapy (PEMF), heat, aquatherapy, balneotherapy, or mud therapy.[19]

Weight loss. The 2012 SR did not consider the effects of weight loss, and no other systematic reviews were identified that assessed the effects of weight loss on the outcomes of interest for this review.

The current review identified moderate-level evidence from RCTs and single-arm trials supporting a beneficial of weight loss on medium-term pain and function and a low level of evidence supporting a beneficial effect of weight loss on long-term pain. Dose-response effects between weight loss and effect sizes were identified for medium-term pain but were inconsistent across most studies.

Home-based and self-management interventions. The 2012 SR included a number of studies that assessed the effects of home-based or self-management interventions but did not

assess these interventions as a category. Two 2015 SRs reviewed the effects of home exercise programs[138] and self-management interventions[139] for the treatment of OA of the knee or knee conditions in general. These SRs reported positive effects of home exercise programs and self-management programs with exercise on pain and function but noted the heterogeneity of interventions and challenges in study design. Most RCTs of exercise interventions included in the current report expected participants to perform exercises at home, but the studies we analyzed in this category explicitly assessed home-based or self-management programs. These programs showed beneficial effects on short-term pain, and medium-term pain and function.

Adverse events. The 2007 SR reported that, in general, adverse events (AEs) for glucosamine with or without chondroitin did not differ between treatment and placebo groups, and no SAEs were reported. Likewise, the 2012 SR on physical interventions reported that AEs did not differ significantly between treatment and control groups and did not deter individuals from continued participation in trials. Approximately half of the studies included in the current review reported having assessed AEs. However, this number includes studies that simply reported that no AEs were found. Of the 13 RCTS that mentioned SAEs, most reported no SAEs or SAEs that could not be attributed to the intervention. Of note, AEs associated with glucosamine and chondroitin did not differ between groups in the placebo-controlled or noninferiority trials. WBV, which was not assessed in the 2012 SR, was not associated with any AEs. PRP was associated with pain and stiffness that increased with the number of injections.

Applicability

The applicability of the results of the trials included in the current review may be somewhat limited for several reasons.

First, the studies of glucosamine and chondroitin used forms and preparations of the dietary supplements that are not available commercially. In addition, the composition and purity of these supplements could be rigorously tested and ensured, unlike most commercial-grade supplements.

Likewise, the studies of PRP each prepared their material using proprietary processes, although at least one publication described the process.

As we discuss further below in the section on limitations of the literature, the results of studies of physical interventions may be influenced heavily by the ability of academic research centers to recruit highly motivated study participants. Even so, much of the success of such interventions in the community is likely to depend on the compliance of patients not only with respect to attending clinic appointments but also with their engaging in regular workouts away from the clinic. Only a small proportion of the studies were considered community based, and even those tend to attract the most motivated participants.

Implications for Clinical and Policy Decisionmaking

OA of the knee is an increasingly prevalent, progressively debilitating condition. Decisions regarding therapies for OA of the knee depend on a number of factors. Patient preferences have the strongest influence and are based on a combination of pain and perceived functional limitations and their influence on quality of life. Treatments for the condition range from the most minimal and least invasive (dietary supplements and over-the-counter analgesics) to total knee replacement. The current report considered only a subset of available interventions, and all fell along the less invasive end of the continuum.

A number of the interventions assessed in the report showed short- or medium-term benefit but either were not assessed sufficiently over the long term (meaning after a long intervention or after

a shorter intervention with a long follow-up time, e.g., Tai chi, TENS, or PRP) or showed minimal benefits in the long term (e.g., glucosamine chondroitin). Several interventions showed beneficial long-term effects, including weight loss and several forms of physical activity (e.g., general exercise programs of the type taught by physical therapists). Because of study design and the numbers and duration of studies, it is not clear which physical activities are most effective, whether they are most effective in combination, or if benefit depends entirely on the individual patient. Adherence, which is obviously an important factor, was seldom assessed in the studies that met inclusion criteria.

One intervention that showed some medium-term benefit, intraarticular injection of PRP, has undergone limited testing for OA of the knee, especially regarding the effects of repeated injections. In addition, this intervention may not currently be covered by most insurers and its use as an intraarticular injection is considered off label by the FDA.

Pending longer RCTs of therapies that show promise for benefits in the short term, the implementation of progressive treatment plans, guided entirely by patient preference is supported by the findings of this review.

Limitations of the Evidence Base

Limitations due to study quality. The results of the RoB assessments for each study appear in Table F1 in Appendix F of the report. In the Results section of the full report, we have provided summary RoB scores for each study. The most prevalent limit to study quality was participant blinding: Only 33 of 85 RCTs reported an attempt to blind participants appropriately, using sham injections, placebo pills, sham applications of a treatment such as TENS, or in the case of exercise interventions, a control condition that could be considered an intervention itself. Many RCTs of physical interventions reported that participants were not or could not be blinded. Although outcome assessors were often reported to have been blinded in these studies, many of the outcomes of interest to this report were self-assessed (such as pain and WOMAC function). This lack of blinding significantly limits conclusions we can draw from the literature and is further discussed below in regard to comparators.

Another quality issue is the large number of RCTs for which adequate concealment of allocation could not be ascertained: 46 of 85. The inability to ascertain allocation concealment might sometimes be attributed to word limitations in publications, but is still a concern.

A third quality concern is the finding that 41 studies did not indicate use of intent-to treat analysis; since participants who are not experiencing benefit from treatment are more likely to drop out before study completion, per protocol analysis could artificially inflate apparent effects.

Fourth, 31 RCTs indicated evidence of incomplete adherence. This figure is actually deceptively low, as most interventions involving exercise require that participants work out on their own on days when they are not being supervised. Most studies did not attempt to monitor offsite compliance, and no studies assessed the effect of such compliance or adherence on outcomes.

Finally, although most studies demonstrated that participants were similar at baseline, some similarities were not routinely considered, such as weight status, or disease stage or severity, and almost no studies stratified outcomes by any baseline characteristics.

Additional limitations. The applicability of the findings of many of the studies to community settings may be limited by their having been conducted in an academic setting and enrolling highly motivated participants. For this reason, we attempted to assess the effects of home-based

interventions; however, these interventions are limited in number, and also tend to be highly supervised. Related to this concern, compliance or adherence was almost never reported.

The applicability of studies of the dietary supplements, glucosamine and chondroitin, may be limited as they either did not report sources, did not ensure purity and concentration of active ingredients, or used forms and preparations that are not available commercially. Likewise, the studies of PRP each prepared their material using proprietary processes, although at least one publication described the process.

Another intervention-related limitation concerns the fact that many studies employed (or failed to prevent) multicomponent interventions. We purposely excluded studies whose multicomponent intervention design precluded assessment of the effect of a single component of interest. However, studies of physical modality interventions often implemented or focused on one type of activity added to a regimen of other activities (with the control group receiving the "other activities" only). In addition, many of the studies permitted continued use of analgesics or other treatments, preventing attribution of improvement to a specific intervention (or blunting the potential effects of an intervention). This problem is discussed further below.

Duration of interventions and followup was a concern. We limited inclusion to studies with a minimum followup of four weeks, because OA of the knee is a chronic, progressive condition. This decision had several implications; for example, no studies of taping met inclusion criteria, as the follow-up time was usually brief. Also, we did not consider the duration of an intervention as an inclusion criterion (as interventions such as PRP injection have no duration). Thus, the interval between the end of an intervention and outcome assessment, especially medium- or long-term followup, differed across studies. In categorizing studies by the length of followup times for potential pooling, we did not always consider the duration of the intervention, itself. This limitation could explain a lack of significant medium- and long-term effects, as few, if any, of the interventions included in this report are thought to have disease-modifying effects that last beyond the intervention.

A related limitation concerns the lack of sufficient numbers of studies with similar interventions to enable assessment of the effects of dose (or intensity, frequency, and duration of physical activity sessions). A 2015 Cochrane review found no evidence for significant differences in the effects of low vs. high intensity interventions on knee or hip OA patients but regarded that the evidence was insufficient to draw firm conclusions.[140]

Another major challenge concerns the choice of study comparators. Contributing to this challenge is the self-reported, subjective nature of pain as an outcome. The placebo effect observed in large placebo-controlled RCTs of glucosamine with or without chondroitin diminished the effect of the active intervention. At the same time, a recent trial comparing glucosamine plus chondroitin to an NSAID found comparable beneficial effects of both. For the current report, we excluded studies that used only comparators of unclear efficacy (e.g., HA as a comparator for PRP) to make it possible to discern the magnitude of the placebo effect. We also excluded studies that used a participant's less-painful knee as the comparator. However, the selection of appropriate comparators is a concern, particularly for studies of physical interventions such as strength training. Many of the studies we included employed usual care as a control; however, as described above, usual care often included a physical therapy program (usually some combination of strength and agility exercises and manipulation). Therefore, the failure to see a difference in outcomes between an intervention and a usual care control group might be attributable to there simply being a limit to the improvement that might be possible over that from standard physical therapy (especially over the often short duration of a study, and without major effort being

expended by participants to work out on their own on days they do not attend the study classes). This conclusion is particularly likely, given that most studies that reported no differences in outcomes between interventions and active controls did report significant improvements from baseline. It is unclear what the most appropriate control is for studies of physical interventions or even studies of weight loss that include exercise: the findings of studies that compared diet alone to exercise and to diet plus exercise were difficult to interpret because exercise might have the same beneficial effects as weight loss, and whether they are synergistic or one actually masks the other could not be determined. That some studies used only active comparators while others used only inactive comparators also limited the numbers of studies that could be pooled or even compared.

A number of outcomes of interest were not reported in the included studies or were reported only sporadically. Risk for undergoing TKR was a prespecified outcome of interest in only one RCT. Many factors that cannot be accounted for influence the decision to undergo TKR. Thus, TKR has not proven to be a useful outcome for assessing the effectiveness of interventions.

We ideally hoped to assess the clinical as well as the statistical significance of any beneficial findings. To do so, we would assess whether statistically significant outcomes met a prespecified minimum clinically important difference (MCID). However, we encountered several major challenges in trying to do so. First, some publications failed to include the numerical scales used with their assessment tools. As a result, it was impossible to assess the potential clinical significance of their findings. Second, published MCIDs depend on the disease severity of the participants; the included studies varied widely in the disease severity of included participants, and some did not report it. Nevertheless, a wide variety of MCIDs have been derived and applied in reviews of similar patient populations (see Appendix I for a summary of published values). We selected and applied one set of values that has been applied in a number of similar reviews[141] to the small number of statistically significant outcomes for which we had pooled standardized mean differences or for which we were able to identify the numerical measurement scales. But, thirdly, it is important to note that MCIDs are derived by translating patients' responses on a scale of multiple items (e.g., the full WOMAC scale contains 24 items), each item graded using numerical rating scales of 4-100 points, to their response to a small number of subjective anchoring question; thus, their validity continues to be debated. Further, in studies with continuous outcomes, even if the mean difference is less than the MCID, a proportion of participants experience outcomes that exceed the MCID. Thus rigorously applying the MCID could prevent patients from obtaining potentially effective treatments.

Small sample size was an additional limitation of concern for many of the studies we identified. For such studies, the importance of significant findings cannot be assured.

Finally, because of the heterogeneity among studies with regard to interventions, comparators, outcome measures, durations of treatment and followup, and even reporting of the scales used for some outcome measures, few studies could be pooled. Although, we describe each study narratively in the report, the inability to pool results limits our confidence in the strength of evidence.

Future Research Recommendations

In general, future studies need to enroll sufficient numbers of participants to enable prespecified subgroup analysis according to important participant characteristics and to enable assessment of both statistical and clinical improvement. Studies also need to employ designs that permit assessing the effects of specific interventions and to consider including both active (sham)

and passive comparison groups to enable participant blinding. Isolation of the interventions being assessed needs to be accomplished both by careful design of the interventions themselves and by prohibiting participants from using alternative modes of therapy. In addition, many interventions need to be conducted for longer durations and mechanisms need to be developed to better measure compliance. Reported outcomes need to include the percent of participants who experience improvement as well as an estimate of whether the effect size achieves a MCID. In addition, the use of imaging and other nonclinical measures will help clarify structure-function relationships and outcomes of interventions.

Recent OARSI guidelines on design of clinical trials for knee OA therapies include 25 recommendations. Among them are clear definition (of and rational for) inclusion/exclusion criteria; assessment and reporting of disease severity; ensuring randomization, blinding (to the extent possible), and similarity of important characteristics at baseline; use of validated outcome measures and steps to minimize bias in patient-reported outcomes.[142] Recommendations specific to particular interventions are described below.

Cell-based therapies. Based on our finding of a significant effect of PRP in a small number of small, high RoB studies, and the number of studies that did not meet inclusion criteria because they compared PRP only to HA, we believe a large, saline-controlled trial is needed. Although corticosteroids could provide an additional comparator for noninferiority, the immediate adverse effects of intraarticular injection of corticosteroids would be impossible to mask. Residual benefits that remain after the intervention is discontinued (and the effect of follow up treatment) also need to be assessed.

In addition, no studies of stem-cell therapy or other cell-based therapies met inclusion criteria. A large multisite commercial clinic that was contacted for trial results did not respond to the request. Clinicaltrials.gov lists several registered trials of stem-cell treatments for OA of the knee, which should be monitored for published findings. We also identified four published studies of gene therapies (using autologous chondrocytes genetically modified to deliver a growth factor and designed to be injected intraarticularly), which to date, have been tested only in Phase II trials.[143-146]

Glucosamine with or without chondroitin. The 2016 MOVES Trial found significant beneficial medium-term effects on pain, function, stiffness, and quality of life for a prescription form of glucosamine hydrochloride plus chondroitin that were comparable with those of a Cox-2 inhibitor in a large patient population with severe pain. The rate of AEs was relatively small and similar across groups (individuals with cardiovascular conditions were excluded). Thus far, longer-term outcomes have not been reported but would need to be considered in formulating guidelines regarding the use of a prescription grade form of the supplement, especially in light of the findings of the LEGS Trial that glucosamine, chondroitin, and the combination had no beneficial effects at 1 and 2 years compared with placebo. In addition, a head-to-head trial similar to MOVES should be conducted using a combination of glucosamine sulfate and chondroitin, as some evidence has suggested glucosamine sulfate is more effective than glucosamine hydrochloride.

Physical interventions. The studies on strength, agility, and aerobic training that met inclusion criteria usually combined the training modality that was being tested with additional exercises, for example, a strength training intervention would include aerobic exercise as a warm-up and would sometimes include a brief session of exercises aimed at improving agility or gait as well. This design matches the physical therapy regimens in current use and probably makes sense as a therapeutic regimen, but it requires that studies that aim to test a specific modality are

carefully designed to ensure that the results can be attributed to the intervention being tested. Other SRs have also noted the difficulty in drawing conclusions regarding the clinical utility of various physical interventions.

Studies are needed to assess the effects of varying the "dose" of physical interventions, by comparing different numbers, durations, and/or intensities of treatments.

The efficacy of individually tailored multicomponent interventions also needs to be assessed but traditional clinical trial methods may not be well-suited to assess such interventions, because testing custom interventions essentially requires that patients serve as their own controls. A number of the trials included in our review modified interventions based on an assessment of individual participant deficits but only one assessed the effects of doing so and found no differences from participants who received a nontailored therapy.

Only one study of aquatherapy, and few studies of yoga or tai chi, met inclusion criteria. Larger trials of these interventions alone compared with both active comparators (to mask the intervention of interest) and waiting list (or other passive) comparators are needed, as they can easily be undertaken by sedentary individuals with no prior training.

OARSI recently published guidelines for the design and conduct of clinical trials of rehabilitation interventions, which include the physical interventions.[142, 147] Recommendations are similar to those of the OARSI guidelines for assessing interventions for OA of the knee.[142] Emphasis is on participant blinding when possible; assessor blinding; use of both sham (active) and passive comparators; description of baseline severity (with clinical measures, if desired); prespecification of adverse events for assessment; use of valid outcome measures with a benchmark, if possible; and assessment of the percent of participants who achieve improvement. Comparative effectiveness trials are advocated for testing novel treatments against those with established effectiveness or when blinding is not otherwise possible. Caution is suggested in applying published MCIDs, as they have been shown to differ by population and other factors.[148]

Weight loss. This review showed beneficial effects of weight loss interventions on pain and function. Future studies need to clarify the roles of exercise and self-efficacy education in the observed effect to assess whether exercise and/or self-efficacy have their own effects, independent of caloric restriction and weight loss or if these co-interventions assist with weight loss and weight maintenance.

The OARSI recently released guidelines on design and conduct of diet and exercise interventions for OA.[147] Most of the recommendations were similar to those provided for rehabilitation and for OA of the knee interventions in general, in copublications. However, they also provided several additional noteworthy recommendations. These include the need to determine in Phase 1 trials whether high-intensity strength training, aimed at increasing quadriceps muscle strength, is safe in older adults with knee OA. Also recommended is allowing monitored use of rescue medication (analgesics), as weight loss trials tend to be longer in duration than other studies.

Home-based therapies. Our results, based on only a small number of studies, suggest home-based therapies with periodic supervision show beneficial effects on pain and function. This model has the advantage of requiring few clinic visits but the disadvantages of lack of monitoring of compliance and correct form when performing activities. The 2016 SR of home-based therapies by Anwer and colleagues also cites the issue of difficulty assessing compliance with home-based interventions.[138] Future research studies of home-based exercise could easily employ any one of a number of fitness monitoring devises to assess adherence and could use applications like Skype to periodically monitor performance.

Adverse effects. Future studies need to prespecify AEs of concern. Researchers need to actively and systematically collect information on adverse effects of interventions at defined intervals, particularly for cell-based therapies and intensive exercise programs.

Finally, because of the heterogeneity among studies with regard to interventions, comparators, outcome measures, and even reporting of the scales used for some outcome measures, few studies could be pooled. Therefore, no attempt could be made to assess whether any pooled effect sizes met or exceeded established MCIDs or MCIIs. For that reason, when individual studies reported their findings in those terms, we attempted to capture those data.

Conclusions

Among the interventions assessed in this report, many had insufficient evidence to determine their benefit for managing OA of the knee. Interventions that show beneficial effects on short-term outcomes of interest include TENS (moderate strength of evidence [SoE]), agility training, home-based programs, and PEMF on pain (low SoE); Tai chi on pain and function; and strength and resistance training on WOMAC total scores (low SoE).

Interventions that show beneficial effects on medium-term outcomes include weight loss for pain (moderate SoE) and function, intraarticular platelet-rich plasma on pain and quality of life, glucosamine plus chondroitin on pain and function, chondroitin sulfate alone on pain, general exercise programs on pain and function, Tai chi on pain and function, whole-body vibration on function, and home-based programs on pain and function (low SoE).

Interventions that show beneficial long-term effects include agility training and general exercise programs for pain and function, and manual therapy and weight loss for pain (low SoE). A moderate SoE supports a lack of long-term benefit of glucosamine-chondroitin on pain or function, and glucosamine or chondroitin sulfate alone on pain.

Insufficient evidence was found for long-term effects of most interventions, and for additional outcomes, such as stiffness, swelling, quality of life, and avoidance of knee replacement, for most interventions.

Larger randomized controlled trials are needed, with more attention to appropriate comparison groups and longer duration, to assess newer therapies and to determine which types of interventions are most effective for which patients.

Table 2. Summary strength of evidence

Intervention/ Follow-up	Pain	Function	WOMAC Total	Quality of Life	Other
Platelet-rich plasma					
Short-term	I (2)	I (2)	I(2)	I(1)	
Medium-term	⇧**L** (4)	I	I(2)	⇧**L**(3)	
Long-term	I (0)	I (0)		I (0)	
Glucosamine with or without chondroitin					
Glucosamine plus chondroitin					
Short -term	I(0)	I(0)		I(0)	
Medium-term	⇧**L(3)***	⇧**L(3)***		NR	
Long-term pain	⇩M (3)[#]	⇩M(3)[#]			
Glucosamine					
Short-term	I(0)	I(0)		I(0)	
Medium-term	I(0)	I(0)		I(0)	
Long-term	⇩M (3)	⇩M (3)			TKR risk ⇧**L(2)**
Chondroitin-sulfate					
Short-term	I(1)	I(1)		I(1)	
Medium-term	⇧**L(2)**	I(2)		I(0)	
Long-term	⇩M (3)	⇩L (2)		I(0)	
Aerobic Exercise					
Short-term	I(1)	I(1)	I(1)		
Medium-term	I(2)	I(2)	I(1)		
Long-term	I(2)	⇩L (3)			
Strength/resistance Training					
Short-term	⇩L(5)[#]	⇩L(5)[#]	⇧**L(3)**		
Medium-term	I(2)	⇩L(3)[#]	I(2)		
Long-term	I(1)	I(1)	I(1)		
Agility Training					
Short-term pain	⇧**L(3)** †	⇩L (3)	I(1)		
Medium-term	⇩L (3)	⇩L (3)			
Long-term	⇧**L(3)**	⇧**L(2)**			
General Exercise					
Short-term	I(1)	I(1)	⇩L (2)	⇩L (2)	
Medium-term	⇧**L(2)**	⇧**L(2)**			
Long-term	⇧**L(3)**	I(2)	I(2)	⇩L (3)	TUG, ⇧L(3)
Tai Chi					
Short-term	⇧**L(3)**	⇧**L(3)**			
Medium-term	⇧**L(2)**	⇧**L(2)**			
Long-term	I(1)	I(1)			
Yoga					
Short-term	I(1)				
Manual Therapy					
Short-term	⇩L(3)[#]	⇩L (4)	I(4)		
Medium-term	I(4)	I(4)	⇩L(3)		
Long-term	⇧**L(2)**	I(0)	I(1)		
Balneotherapy and Mud Therapy					
Balneotherapy					
Short-term	I(0)	I(0)			
Medium-term pain	⇧**L(2)**	⇧**L(2)**			
Topical Mud therapy					
All durations	I(0)	I(0)			
Mud bath therapy					
All durations	I(0)	I(0)			
Heat, Infrared Ultrasound					
Heat or infrared					
All durations	I(3)	I(3)	I(3)		
Ultrasound					

Intervention/ Follow-up	Pain	Function	WOMAC Total	Quality of Life	Other
Short-term	I(2)	I(1)	I(1)		
Medium-term	I(1)	I(1)			
Long-term	I(1)	I(1)			
Pulsed Electromagnetic Field					
Short-term	⇧**L(3)** #	I(1)	I(1)		
Medium-term	I(0)	I(0)			
Long-term	I(0)	I(0)			
Transcutaneous Electrical Nerve Stimulation (TENS)					
Short-term	⇧**M(4)** ₴	⇩L (3)	⇩L (3)		
Medium-term	⇩L(2)	⇩L(2)	I(1)		
Long-term	I(0)	I(0)			
Neuromuscular Electrical Stimulation (NMES)					
Short-term	I(2)	I(0)			
Medium-term	I(2)	I(0)			
Whole-body Vibration(WBV)					
Short-term	⇩L(3)	I(1)	I(2)	I(1)	I(3)
Medium-term	⇩L(4) #	⇧**L(4)** # ₴			⇩L(4) # 6' walk
Orthoses (Braces, Shoe Inserts, and Custom Shoes)					
Braces					
Short-term	I(1)	I(0)			
Medium-term	I(1)	I(0)			
Long-term	I(1)	I(0)			
Shoe inserts					
Short-term	⇩L(4)	⇩L(3)	⇩L(3) #		
Medium-term	⇩L(3) #	⇩L(4)	I(1)		
Long-term	I(2)	I(2)			
Custom Shoes					
Short-term	I(0)	I(0)			
Medium-term	I(2)	I(1)	I(1)		
Long-term	I(1)	I(0)			
Cane					
Short-term	I(1)	I(1)	I(1)		
Weight loss					
Short-term	I(2)	I(2)			
Medium-term pain	⇧**M(6)****	⇧**L(6)****	I(1)		
Long-term	⇧**L(4)****	I(2)	I(1)		
Home-based and Self-Management Programs					
Short-term	⇧**L(2)**	I(2)	⇧**L(2)**		
Medium-term	⇧**L(3)**	⇧**L(4)**	I(1)		I(2)
Long-term	I(1)	I(2)		I(1)	I(1)
Key Question 2 Adverse Events					⇩M SAEs and nonSAEs

Table Notes: Blank spaces=outcome not reported; ⇧=beneficial effect; ⇩=no beneficial effect; L=low strength of evidence; M=moderate strength of evidence; I=insufficient evidence; (n)=number of trials that met inclusion criteria; TKR=total knee replacement risk; *Beneficial effect vs. analgesic or placebo; #Pooled analysis; †compared with placebo but not strength training; ₴Did not meet MCID; **RCTs and single-arm trials.

References

1. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum. 2008 Jan;58(1):26-35. doi: 10.1002/art.23176. PMID: 18163497.

2. Dillon CF, Rasch EK, Gu Q, et al. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991-94. J Rheumatol. 2006 Nov;33(11):2271-9. doi: 06/13/1011 [pii]. PMID: 17013996.

3. Richmond SA, Fukuchi RK, Ezzat A, et al. Are Joint Injury, Sport Activity, Physical Activity, Obesity, or Occupational Activities Predictors for Osteoarthritis? A Systematic Review. J Orthop Sports Phys Ther. 2013 Jun 11doi: 2900 [pii]10.2519/jospt.2013.4796. PMID: 23756344.

4. Murphy L, Schwartz TA, Helmick CG, et al. Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum. 2008 Sep 15;59(9):1207-13. doi: 10.1002/art.24021. PMID: 18759314.

5. Weinstein AM, Rome BN, Reichmann WM, et al. Estimating the burden of total knee replacement in the United States. J Bone Joint Surg Am. 2013 Mar 6;95(5):385-92. doi: 1555390 [pii]10.2106/JBJS.L.00206. PMID: 23344005.

6. Teichtahl AJ, Wluka AE, Wang Y, et al. The longitudinal relationship between changes in body weight and changes in medial tibial cartilage, and pain among community-based adults with and without meniscal tears. Ann Rheum Dis. 2013 Jun 6doi: annrheumdis-2013-203210 [pii]10.1136/annrheumdis-2013-203210. PMID: 23744978.

7. Samson DJ, Grant MD, Ratko TA, et al. Treatment of primary and secondary osteoarthritis of the knee. Evidence Report/Technology Assessment No. 157 (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-02-0026) Agency for Healthcare Research and Quality. Rockville, MD: September 2007.

8. Schiphof D, de Klerk BM, Kerkhof HJ, et al. Impact of different descriptions of the Kellgren and Lawrence classification criteria on the diagnosis of knee osteoarthritis. Ann Rheum Dis. 2011 Aug;70(8):1422-7. doi: ard.2010.147520 [pii] 10.1136/ard.2010.147520. PMID: 21555325.

9. Cibere J, Zhang H, Thorne A, et al. Association of clinical findings with pre-radiographic and radiographic knee osteoarthritis in a population-based study. Arthritis Care Res (Hoboken). 2010 Dec;62(12):1691-8. doi: 10.1002/acr.20314. PMID: 20665737.

10. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012 Apr;64(4):465-74. PMID: 22563589.

11. American Academy of Orthopaedic Surgeons. Treatment of Osteoarthritis of the Knee, 2nd Edition: SUMMARY OF RECOMMENDATIONS. http://www.aaos.org/research/guidelines/OAKSummaryofRecommendations.pdf.

12. Newberry SJ, FitzGerald JD, Maglione M, et al. Systematic Review for Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee. (Prepared by the Southern California Evidence-based Practice Center). Technology Assessment Report. AHRQ. Project ID: DJDTO913. In preparation.

13. Shamliyan TA, Wang SY, Olson-Kellogg B, et al. Physical Therapy Interventions for Knee Pain Secondary to Osteoarthritis. Rockville (MD): Agency for Healthcare Research and Quality; 2012.

14. Chou R, McDonagh MS, Nakamoto E, et al. Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review.

Comparative Effectiveness Review No. 38. (Prepared by the Oregon Evidence-based Practice Center under Contract No. HHSA 290 2007 10057 I) Agency for Healthcare Research and Quality. Rockville, MD: October 2011.

15. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2014. p. Chapters available at: www.effectivehealthcare.ahrq.gov.

16. Osteoarthritis of the Knee. Draft Key Questions. Rockville, MD: AHRQ Effective Health Care Program; 2015. http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displaytopic&topicid=633. Accessed on March 7 2016.

17. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum. 1986 Aug;29(8):1039-49. PMID: 3741515.

18. Whitlock EP, Lin JS, Chou R, et al. Using existing systematic reviews in complex systematic reviews. Ann Intern Med. 2008 May 20;148(10):776-82. PMID: 18490690.

19. Shamliyan TA, Wang SY, Olson-Kellogg B, et al. AHRQ Comparative Effectiveness Reviews. Physical Therapy Interventions for Knee Pain Secondary to Osteoarthritis. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012.

20. Armijo-Olivo S, da Costa BR, Cummings GG, et al. PEDro or Cochrane to Assess the Quality of Clinical Trials? A Meta-Epidemiological Study. PLoS One. 2015;10(7):e0132634. doi: 10.1371/journal.pone.0132634. PMID: 26161653.

21. Whiting P, Savovic J, Higgins JP, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016 Jan;69:225-34. doi: 10.1016/j.jclinepi.2015.06.005. PMID: 26092286.

22. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol. 2014;14:25. doi: 10.1186/1471-2288-14-25. PMID: 24548571.

23. Patel S, Dhillon MS, Aggarwal S, et al. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Med. 2013 Feb;41(2):356-64. doi: 10.1177/0363546512471299. PMID: 23299850.

24. Gormeli G, Gormeli CA, Ataoglu B, et al. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. Knee Surg Sports Traumatol Arthrosc. 2015 Aug 2doi: 10.1007/s00167-015-3705-6. PMID: 26233594.

25. Rayegani SM, Raeissadat SA, Taheri MS, et al. Does intra articular platelet rich plasma injection improve function, pain and quality of life in patients with osteoarthritis of the knee? A randomized clinical trial. Orthop Rev (Pavia). 2014 Aug 8;6(3):5405. doi: 10.4081/or.2014.5405. PMID: 25317308.

26. Acosta-Olivo C, Esponda-Colmenares F, Vilchez-Cavazos F, et al. Platelet rich plasma versus oral paracetamol for the treatment of early knee osteoarthritis. Preliminar study. Cirugia y Cirujanos. 2014;82(2):163-9.

27. Simental-Mendia M, Vilchez-Cavazos JF, Pena-Martinez VM, et al. Leukocyte-poor platelet-rich plasma is more effective than the conventional therapy with acetaminophen for the treatment of early knee osteoarthritis. Arch Orthop Trauma Surg. 2016 Aug 9doi: 10.1007/s00402-016-2545-2. PMID: 27506585.

28. Sawitzke AD, Shi H, Finco MF, et al. Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. Ann Rheum Dis. 2010 Aug;69(8):1459-64. doi: 10.1136/ard.2009.120469. PMID: 20525840.

29. Hochberg MC, Martel-Pelletier J, Monfort J, et al. Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: A multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. Annals of the Rheumatic Diseases. 2016;75:37-44. PMID: 2015073670 FULL TEXT LINK http://dx.doi.org/10.1136/annrheumdis-2014-206792.

30. Bellare N, Argekar H, Bhagwat A, et al. Glucosamine and chondroitin sulphate supplementation along with diet therapy provides better symptomatic relief in osteoarthritic patients as compared to diet therapy alone. International Journal of Pharmaceutical Sciences Review and Research; 2014. p. 215-23.

31. Fransen M, Agaliotis M, Nairn L, et al. Glucosamine and chondroitin for knee osteoarthritis: A double-blind randomised placebo-controlled clinical trial evaluating single and combination regimens. Annals of the Rheumatic Diseases. 2014;6.

32. Herrero-Beaumont G, Roman-Blas J, Castaneda S, et al. Chondroitin sulfate plus glucosamine sulfate does not show superiority over placebo in a randomised, double blind, placebo-controlled clinical trial in patients with knee osteoarthritis. Osteoarthritis and cartilage; 2016. p. S48-s9.

33. Bruyere O, Pavelka K, Rovati LC, et al. Total joint replacement after glucosamine sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients from two previous 3-year, randomised, placebo-controlled trials. Osteoarthritis Cartilage. 2008 Feb;16(2):254-60. doi: 10.1016/j.joca.2007.06.011. PMID: 17681803.

34. Stambolova Ivanova MP. Maintenance therapy with glucosamine sulfate and physiotherapy on osteoarthritis progression. Osteoporosis International. 2015 February;26(1 SUPPL. 1):S116-S7.

35. Pavelka K, Gatterova J, Olejarova M, et al. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med. 2002 Oct 14;162(18):2113-23. PMID: 12374520.

36. Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet. 2001 Jan 27;357(9252):251-6. doi: 10.1016/S0140-6736(00)03610-2. PMID: 11214126.

37. Zegels B, Crozes P, Uebelhart D, et al. Equivalence of a single dose (1200 mg) compared to a three-time a day dose (400 mg) of chondroitin 4&6 sulfate in patients with knee osteoarthritis. Results of a randomized double blind placebo controlled study. Osteoarthritis Cartilage. 2013 Jan;21(1):22-7. doi: 10.1016/j.joca.2012.09.017. PMID: 23059756.

38. Kahan A, Uebelhart D, De Vathaire F, et al. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2009 Feb;60(2):524-33. doi: 10.1002/art.24255. PMID: 19180484.

39. Brosseau L, Wells GA, Kenny GP, et al. The implementation of a community-based aerobic walking program for mild to moderate knee osteoarthritis: a knowledge translation randomized controlled trial: part II: clinical outcomes. BMC Public Health. 2012;12:1073. doi: 10.1186/1471-2458-12-1073. PMID: 23234575.

40. Samut G, Dincer F, Ozdemir O. The effect of isokinetic and aerobic exercises on serum interleukin-6 and tumor necrosis factor alpha levels, pain, and functional activity in patients with knee osteoarthritis. Mod Rheumatol. 2015 May 27:1-6. doi:

10.3109/14397595.2015.1038425. PMID: 25849853.

41. Koli J, Multanen J, Kujala UM, et al. CLINICAL SCIENCES Effects of Exercise on Patellar Cartilage in Women with Mild Knee Osteoarthritis. Medicine & Science in Sports & Exercise. 2015 September 2015;47(9) PMID: 109090545.

42. Schlenk EA, Lias JL, Sereika SM, et al. Improving physical activity and function in overweight and obese older adults with osteoarthritis of the knee: a feasibility study. Rehabil Nurs. 2011 Jan-Feb;36(1):32-42. PMID: 21290963.

43. Salacinski AJ, Krohn K, Lewis SF, et al. The effects of group cycling on gait and pain-related disability in individuals with mild-to-moderate knee osteoarthritis: a randomized controlled trial. J Orthop Sports Phys Ther. 2012 Dec;42(12):985-95. doi: 10.2519/jospt.2012.3813. PMID: 22951360.

44. Bruce-Brand RA, Walls RJ, Ong JC, et al. Effects of home-based resistance training and neuromuscular electrical stimulation in knee osteoarthritis: a randomized controlled trial. BMC Musculoskelet Disord. 2012;13:118. doi: 10.1186/1471-2474-13-118. PMID: 22759883.

45. Wortley M, Zhang S, Paquette M, et al. Effects of resistance and Tai Ji training on mobility and symptoms in knee osteoarthritis patients. Journal of Sport and Health Science; 2013. p. 209-14.

46. Rogers MW, Tamulevicius N, Semple SJ, et al. Efficacy of home-based kinesthesia, balance & agility exercise training among persons with symptomatic knee osteoarthritis. J Sports Sci Med. 2012;11(4):751-8. PMID: 24150088.

47. Oliveira AM, Peccin MS, Silva KN, et al. Impact of exercise on the functional capacity and pain of patients with knee osteoarthritis: a randomized clinical trial. Rev Bras Reumatol. 2012 Dec;52(6):876-82. PMID: 23223698.

48. Imoto AM, Peccin MS, Trevisani VF. Quadriceps strengthening exercises are effective in improving pain, function and quality of life in patients with osteoarthritis of the knee. Acta Ortop Bras. 2012;20(3):174-9. doi: 10.1590/s1413-78522012000300008. PMID: 24453599.

49. Jorge RTB, de Souza MC, Chiari A, et al. Progressive resistance exercise in women with osteoarthritis of the knee: a randomized controlled trial. Clinical Rehabilitation. 2015 Mar;29(3):234-43. doi: 10.1177/0269215514540920. PMID: WOS:000352000500004.

50. Singh S, Pattnaik M, Mohanty P, et al. Effectiveness of hip abductor strengthening on health status, strength, endurance and six minute walk test in participants with medial compartment symptomatic knee osteoarthritis. J Back Musculoskelet Rehabil. 2016;29(1):65-75. doi: 10.3233/bmr-150599. PMID: 26406217.

51. Nam CW, Kim K, Lee HY. The influence of exercise on an unstable surface on the physical function and muscle strength of patients with osteoarthritis of the knee. J Phys Ther Sci. 2014 Oct;26(10):1609-12. doi: 10.1589/jpts.26.1609. PMID: 25364125.

52. Foroughi N, Smith RM, Lange AK, et al. Progressive resistance training and dynamic alignment in osteoarthritis: A single-blind randomised controlled trial. Clin Biomech (Bristol, Avon). 2011 Jan;26(1):71-7. doi: 10.1016/j.clinbiomech.2010.08.013. PMID: 20869141.

53. Bennell KL, Ahamed Y, Jull G, et al. Physical therapist-delivered pain coping skills training and exercise for knee osteoarthritis: Randomized controlled trial. Arthritis Care Res (Hoboken). 2015 Sep 28doi: 10.1002/acr.22744. PMID: 26417720.

54. Mangani I, Cesari M, Kritchevsky SB, et al. Physical exercise and comorbidity. Results from the Fitness and Arthritis in Seniors Trial (FAST). Aging Clin Exp Res. 2006 Oct;18(5):374-80. PMID: 17167301.

55. Fitzgerald GK, Piva SR, Gil AB, et al. Agility and perturbation training techniques in exercise therapy for reducing pain and improving function in people with knee osteoarthritis: a randomized clinical trial. Phys Ther. 2011 Apr;91(4):452-69. doi: 10.2522/ptj.20100188. PMID: 21330451.

56. Henriksen M, Klokker L, Graven-Nielsen T, et al. Association of exercise therapy and reduction of pain sensitivity in patients with knee osteoarthritis: a randomized controlled trial. Arthritis Care Res (Hoboken). 2014 Dec;66(12):1836-43. doi: 10.1002/acr.22375. PMID: 24905427.

57. Ju SB, Park GD, Kim SS. Effects of proprioceptive circuit exercise on knee joint pain and muscle function in patients with knee osteoarthritis. J Phys Ther Sci. 2015 Aug;27(8):2439-41. doi: 10.1589/jpts.27.2439. PMID: 26357422.

58. da Silva FS, de Melo FE, do Amaral MM, et al. Efficacy of simple integrated group rehabilitation program for patients with knee osteoarthritis: Single-blind randomized controlled trial. J Rehabil Res Dev. 2015;52(3):309-22. doi: 10.1682/jrrd.2014.08.0199. PMID: 26237073.

59. Barduzzi GO, Rocha Júnior PR, Souza Neto JC, et al. [Functional capacity of elderly with osteoarthritis who undergone to aquatic and land physical therapy]. Fisioterapia em Movimento; 2013. p. 349-60.

60. Segal NA, Glass NA, Teran-Yengle P, et al. Intensive Gait Training for Older Adults with Symptomatic Knee Osteoarthritis. Am J Phys Med Rehabil. 2015 Oct;94(10 Suppl 1):848-58. doi: 10.1097/phm.0000000000000264. PMID: 25768068.

61. Knoop J, Dekker J, van der Leeden M, et al. Knee joint stabilization therapy in patients with osteoarthritis of the knee: a randomized, controlled trial. Osteoarthritis Cartilage. 2013 Aug;21(8):1025-34. doi: 10.1016/j.joca.2013.05.012. PMID: 23721797.

62. Christensen R, Henriksen M, Leeds AR, et al. Effect of weight maintenance on symptoms of knee osteoarthritis in obese patients: a twelve-month randomized controlled trial. Arthritis Care Res (Hoboken). 2015 May;67(5):640-50. doi: 10.1002/acr.22504. PMID: 25370359.

63. Lim JY, Tchai E, Jang SN. Effectiveness of aquatic exercise for obese patients with knee osteoarthritis: a randomized controlled trial. Pm r. 2010 Aug;2(8):723-31; quiz 93. doi: 10.1016/j.pmrj.2010.04.004. PMID: 20709301.

64. Rosedale R, Rastogi R, May S, et al. Efficacy of exercise intervention as determined by the McKenzie System of Mechanical Diagnosis and Therapy for knee osteoarthritis: a randomized controlled trial. J Orthop Sports Phys Ther. 2014 Mar;44(3):173-81, a1-6. doi: 10.2519/jospt.2014.4791. PMID: 24450370.

65. Abbott JH, Chapple CM, Fitzgerald GK, et al. The Incremental Effects of Manual Therapy or Booster Sessions in Addition to Exercise Therapy for Knee Osteoarthritis: A Randomized Clinical Trial. J Orthop Sports Phys Ther. 2015 Sep 28:1-9. doi: 10.2519/jospt.2015.6015. PMID: 26416334.

66. de Rooij M, van der Leeden M, Cheung J, et al. Efficacy of tailored exercise therapy on physical functioning in patients with knee osteoarthritis and comorbidity: A randomized controlled trial. Arthritis Care Res (Hoboken). 2016 Aug 26doi: 10.1002/acr.23013. PMID: 27563831.

67. Fitzgerald GK, Fritz JM, Childs JD, et al. Exercise, manual therapy, and use of booster sessions in physical therapy for knee osteoarthritis: a multi-center, factorial randomized clinical trial. Osteoarthritis Cartilage. 2016 Aug;24(8):1340-9. doi: 10.1016/j.joca.2016.03.001. PMID: 26973326.

68. Bartels EM, Christensen R, Christensen P, et al. Effect of a 16 weeks weight loss program on osteoarthritis biomarkers in obese patients with knee osteoarthritis: a prospective cohort study. Osteoarthritis Cartilage. 2014 Nov;22(11):1817-25. doi:

10.1016/j.joca.2014.07.027. PMID: 25106676.

69. Tsai PF, Chang JY, Beck C, et al. A pilot cluster-randomized trial of a 20-week Tai Chi program in elders with cognitive impairment and osteoarthritic knee: effects on pain and other health outcomes. J Pain Symptom Manage. 2013 Apr;45(4):660-9. doi: 10.1016/j.jpainsymman.2012.04.009. PMID: 23017610.

70. Chenchen W, Schmid CH, Iversen MD, et al. Comparative Effectiveness of Tai Chi Versus Physical Therapy for Knee Osteoarthritis: A Randomized Trial. Annals of Internal Medicine. 2016;165(2):77-86. doi: 10.7326/M15-2143. PMID: 116901077. Language: English. Entry Date: In Process. Revision Date: 20160817. Publication Type: journal article. Journal Subset: Biomedical.

71. Cheung C, Wyman JF, Resnick B, et al. Yoga for managing knee osteoarthritis in older women: a pilot randomized controlled trial. BMC Complement Altern Med. 2014;14:160. doi: 10.1186/1472-6882-14-160. PMID: 24886638.

72. Fioravanti A, Giannitti C, Bellisai B, et al. Efficacy of balneotherapy on pain, function and quality of life in patients with osteoarthritis of the knee. Int J Biometeorol. 2012 Jul;56(4):583-90. doi: 10.1007/s00484-011-0447-0. PMID: 21573819.

73. Kulisch A, Benko A, Bergmann A, et al. Evaluation of the effect of Lake Heviz thermal mineral water in patients with osteoarthritis of the knee: a randomized, controlled, single-blind, follow-up study. Eur J Phys Rehabil Med. 2014 Aug;50(4):373-81. PMID: 24594851.

74. Mahboob N, Sousan K, Shirzad A, et al. The efficacy of a topical gel prepared using Lake Urmia mud in patients with knee osteoarthritis. J Altern Complement Med. 2009 Nov;15(11):1239-42. doi: 10.1089/acm.2009.0304. PMID: 19922256.

75. Fioravanti A, Bacaro G, Giannitti C, et al. One-year follow-up of mud-bath therapy in patients with bilateral knee osteoarthritis: a randomized, single-blind controlled trial. Int J Biometeorol. 2015 Sep;59(9):1333-43. doi: 10.1007/s00484-014-0943-0. PMID: 25516113.

76. Lenssen AF, Crijns YH, Waltje EM, et al. Efficiency of immediate postoperative inpatient physical therapy following total knee arthroplasty: an RCT. BMC Musculoskelet Disord. 2006;7:71. doi: 10.1186/1471-2474-7-71. PMID: 16942627.

77. Yildirim N, Filiz Ulusoy M, Bodur H. The effect of heat application on pain, stiffness, physical function and quality of life in patients with knee osteoarthritis. J Clin Nurs. 2010 Apr;19(7-8):1113-20. doi: 10.1111/j.1365-2702.2009.03070.x. PMID: 20492056.

78. Hsieh RL, Lo MT, Lee WC, et al. Therapeutic effects of short-term monochromatic infrared energy therapy on patients with knee osteoarthritis: a double-blind, randomized, placebo-controlled study. J Orthop Sports Phys Ther. 2012 Nov;42(11):947-56. doi: 10.2519/jospt.2012.3881. PMID: 22960644.

79. Cakir S, Hepguler S, Ozturk C, et al. Efficacy of therapeutic ultrasound for the management of knee osteoarthritis: a randomized, controlled, and double-blind study. Am J Phys Med Rehabil. 2014 May;93(5):405-12. doi: 10.1097/phm.0000000000000033. PMID: 24322433.

80. Carlos KP, Belli BS, Alfredo PP. Effect of pulsed ultrasound and continuous ultrasound linked to exercise in patients with knee osteoarthritis: pilot study. Fisioterapia e Pesquisa; 2012. p. 275-81.

81. Kapci Yildiz S, Unlu Ozkan F, Aktas I, et al. The effectiveness of ultrasound treatment for the management of knee osteoarthritis: a randomized, placebo-controlled, double-blind study. Turkish Journal of Medical Sciences. 2015;45(6):1187-91. doi: 10.3906/sag-1408-81. PMID: WOS:000365510300001.

82. Laufer Y, Shtraker H, Elboim Gabyzon M. The effects of exercise and neuromuscular electrical stimulation in subjects with knee

osteoarthritis: a 3-month follow-up study. Clin Interv Aging. 2014;9:1153-61. doi: 10.2147/cia.s64104. PMID: 25083133.

83. Mizusaki Imoto A, Peccin S, Gomes da Silva KN, et al. Effects of neuromuscular electrical stimulation combined with exercises versus an exercise program on the pain and the function in patients with knee osteoarthritis: a randomized controlled trial. Biomed Res Int. 2013;2013:272018. doi: 10.1155/2013/272018. PMID: 24151589.

84. Imoto AM, Peccin MS, Teixeira LE, et al. Is neuromuscular electrical stimulation effective for improving pain, function and activities of daily living of knee osteoarthritis patients? A randomized clinical trial. Sao Paulo Med J. 2013;131(2):80-7. PMID: 23657509.

85. Elboim-Gabyzon M, Rozen N, Laufer Y. Does neuromuscular electrical stimulation enhance the effectiveness of an exercise programme in subjects with knee osteoarthritis? A randomized controlled trial. Clin Rehabil. 2013 Mar;27(3):246-57. doi: 10.1177/0269215512456388. PMID: 22952305.

86. Gschiel B, Kager H, Pipam W, et al. [Analgesic efficacy of TENS therapy in patients with gonarthrosis. A prospective, randomised, placebo-controlled, double-blind study]. Schmerz. 2010 Sep;24(5):494-500. doi: 10.1007/s00482-010-0957-4. PMID: 20706740.

87. Atamaz FC, Durmaz B, Baydar M, et al. Comparison of the efficacy of transcutaneous electrical nerve stimulation, interferential currents, and shortwave diathermy in knee osteoarthritis: a double-blind, randomized, controlled, multicenter study. Arch Phys Med Rehabil. 2012 May;93(5):748-56. doi: 10.1016/j.apmr.2011.11.037. PMID: 22459699.

88. Palmer S, Domaille M, Cramp F, et al. Transcutaneous electrical nerve stimulation as an adjunct to education and exercise for knee osteoarthritis: a randomized controlled trial. Arthritis Care Res (Hoboken). 2014 Mar;66(3):387-94. doi: 10.1002/acr.22147. PMID: 23983090.

89. Inal EE, Eroglu P, Yucel SH, et al. Which is the Appropriate Frequency of TENS in Managing Knee Osteoarthritis: High or Low Frequency? Journal of Clinical and Analytical Medicine. 2016 May;7(3):339-44. doi: 10.4328/JCAM.3387. PMID: WOS:000376566800013.

90. Nelson FR, Zvirbulis R, Pilla AA. Non-invasive electromagnetic field therapy produces rapid and substantial pain reduction in early knee osteoarthritis: a randomized double-blind pilot study. Rheumatology International. 2013 Aug;33(8):2169-73. PMID: WOS:000322120400037.

91. Dundar U, Asik G, Ulasli AM, et al. Assessment of pulsed electromagnetic field therapy with Serum YKL-40 and ultrasonography in patients with knee osteoarthritis. Int J Rheum Dis. 2015 May 8doi: 10.1111/1756-185x.12565. PMID: 25955771.

92. Bagnato GL, Miceli G, Marino N, et al. Pulsed electromagnetic fields in knee osteoarthritis: a double blind, placebo-controlled, randomized clinical trial. Rheumatology (Oxford). 2016 Apr;55(4):755-62. doi: 10.1093/rheumatology/kev426. PMID: 26705327.

93. Avelar NC, Simao AP, Tossige-Gomes R, et al. The effect of adding whole-body vibration to squat training on the functional performance and self-report of disease status in elderly patients with knee osteoarthritis: a randomized, controlled clinical study. J Altern Complement Med. 2011 Dec;17(12):1149-55. doi: 10.1089/acm.2010.0782. PMID: 22087576.

94. Rabini A, De Sire A, Marzetti E, et al. Effects of focal muscle vibration on physical functioning in patients with knee osteoarthritis: a randomized controlled trial. Eur J Phys Rehabil Med. 2015 Oct;51(5):513-20. PMID: 25990196.

95. Wang P, Yang L, Liu C, et al. Effects of Whole Body Vibration Exercise associated with Quadriceps Resistance Exercise on

functioning and quality of life in patients with knee osteoarthritis: A randomized controlled trial. Clin Rehabil. 2015 Oct 1doi: 10.1177/0269215515607970. PMID: 26427960.

96. Wang P, Yang L, Li H, et al. Effects of whole-body vibration training with quadriceps strengthening exercise on functioning and gait parameters in patients with medial compartment knee osteoarthritis: a randomised controlled preliminary study. Physiotherapy. 2015 May 15doi: 10.1016/j.physio.2015.03.3720. PMID: 26111989.

97. Simao AP, Avelar NC, Tossige-Gomes R, et al. Functional performance and inflammatory cytokines after squat exercises and whole-body vibration in elderly individuals with knee osteoarthritis. Arch Phys Med Rehabil. 2012 Oct;93(10):1692-700. doi: 10.1016/j.apmr.2012.04.017. PMID: 22546535.

98. Park YG, Kwon BS, Park JW, et al. Therapeutic effect of whole body vibration on chronic knee osteoarthritis. Ann Rehabil Med. 2013 Aug;37(4):505-15. doi: 10.5535/arm.2013.37.4.505. PMID: 24020031.

99. Bokaeian HR, Bakhtiary AH, Mirmohammadkhani M, et al. The effect of adding whole body vibration training to strengthening training in the treatment of knee osteoarthritis: A randomized clinical trial. J Bodyw Mov Ther. 2016 Apr;20(2):334-40. doi: 10.1016/j.jbmt.2015.08.005. PMID: 27210851.

100. Callaghan MJ, Parkes MJ. A randomised trial of a brace for patellofemoral osteoarthritis targeting knee pain and bone marrow lesions. 2015 Jun;74(6):1164-70. doi: 10.1136/annrheumdis-2014-206376. PMID: 25596158.

101. Cherian JJ, Bhave A, Kapadia BH, et al. Strength and Functional Improvement Using Pneumatic Brace with Extension Assist for End-Stage Knee Osteoarthritis: A Prospective, Randomized trial. Journal of Arthroplasty. 2015 1;30(5):747-53. PMID: 2014984002 FULL TEXT LINK http://dx.doi.org/10.1016/j.arth.2014.11.036.

102. Sattari S, Ashraf AR. Comparison the effect of 3 point valgus stress knee support and lateral wedge insoles in medial compartment knee osteoarthritis. Iran Red Crescent Med J. 2011 Sep;13(9):624-8. PMID: 22737536.

103. Rodrigues PT, Ferreira AF, Pereira RM, et al. Effectiveness of medial-wedge insole treatment for valgus knee osteoarthritis. Arthritis and rheumatism; 2008. p. 603-8.

104. Koca B, Oz B, Olmez N, et al. Effect of lateral-wedge shoe insoles on pain and function in patients with knee osteoarthritis. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi. 2009 December;55(4):158-62. PMID: 2010074832.

105. Hatef MR, Mirfeizi Z, Sahebari M, et al. Superiority of laterally elevated wedged insoles to neutrally wedged insoles in medial knee osteoarthritis symptom relief. Int J Rheum Dis. 2014 Jan;17(1):84-8. doi: 10.1111/1756-185x.12036. PMID: 24472270.

106. Campos GC, Rezende MU, Pasqualin T, et al. Lateral wedge insole for knee osteoarthritis: randomized clinical trial. Sao Paulo Med J. 2015 Feb;133(1):13-9. doi: 10.1590/1516-3180.2013.6750002. PMID: 25626851.

107. Wallace DA. Efficacy of lateral heel wedge orthotics for the treatment of patients with knee osteoarthritis. Oregon State University. 2006 PMID: 109847445.

108. Toda Y, Tsukimura N. A 2-year follow-up of a study to compare the efficacy of lateral wedged insoles with subtalar strapping and in-shoe lateral wedged insoles in patients with varus deformity osteoarthritis of the knee. Osteoarthritis and Cartilage. 2006 March;14(3):231-7. PMID: 2006107628 MEDLINE PMID 16271485 (http://www.ncbi.nlm.nih.gov/pubmed/16271485) FULL TEXT LINK http://dx.doi.org/10.1016/j.joca.2005.09.006.

109. Bennell KL, Bowles KA, Payne C, et al. Lateral wedge insoles for medial knee osteoarthritis: 12 Month randomised controlled trial. Bmj. 2011;342(7808) PMID: 2011293830 MEDLINE PMID 21593096 (http://www.ncbi.nlm.nih.gov/pubmed/21593096) FULL TEXT LINK http://dx.doi.org/10.1136/bmj.d2912.

110. Goldenstein-Schainberg C, Fuller R, Matias A, et al. Effectiveness of long-term use of minimalist footwear on pain and function in knee osteoarthritis. Osteoporosis international; 2013. p. S139.

111. Trombini-Souza F, Matias A, Yokota M, et al. Beneficial effect of long-term use of a low-cost minimalist footwear on joint load, clinical, and functional aspects of elderly women with knee osteoarthritis. Arthritis and rheumatism; 2013. p. S918.

112. Trombini-Souza F, Matias AB, Yokota M, et al. Long-term use of minimal footwear on pain, self-reported function, analgesic intake, and joint loading in elderly women with knee osteoarthritis: A randomized controlled trial. Clin Biomech (Bristol, Avon). 2015 Aug 14doi: 10.1016/j.clinbiomech.2015.08.004. PMID: 26307181.

113. Erhart JC, Mundermann A, Elspas B, et al. Changes in Knee Adduction Moment, Pain, and Functionality with a Variable-Stiffness Walking Shoe after 6 Months. Journal of Orthopaedic Research. 2010 Jul;28(7):873-9. PMID: WOS:000278654500006.

114. Erhart-Hledik JC, Elspas B, Giori NJ, et al. Effect of variable-stiffness walking shoes on knee adduction moment, pain, and function in subjects with medial compartment knee osteoarthritis after 1 year. J Orthop Res. 2012 Apr;30(4):514-21. doi: 10.1002/jor.21563. PMID: 21953877.

115. Jones A, Silva PG, Silva AC, et al. Impact of cane use on pain, function, general health and energy expenditure during gait in patients with knee osteoarthritis: a randomised controlled trial. Ann Rheum Dis. 2012 Feb;71(2):172-9. doi: 10.1136/ard.2010.140178. PMID: 22128081.

116. Azlin MNN, Lyn KS. Effects of Passive Joint Mobilization on Patients with Knee Osteoarthritis. Sains Malaysiana. 2011 Dec;40(12):1461-5. PMID: WOS:000299019800017.

117. Cheawthamai K, Vongsirinavarat M, Hiengkaew V, et al. A comparison of home-based exercise programs with and without self-manual therapy in individuals with knee osteoarthritis in community. J Med Assoc Thai. 2014 Jul;97 Suppl 7:S95-100. PMID: 25141536.

118. Cortes Godoy V, Gallego Izquierdo T, Lazaro Navas I, et al. Effectiveness of massage therapy as co-adjuvant treatment to exercise in osteoarthritis of the knee: a randomized control trial. J Back Musculoskelet Rehabil. 2014;27(4):521-9. doi: 10.3233/bmr-140476. PMID: 24867903.

119. Zhang Y, Shen CL, Peck K, et al. Training Self-Administered Acupressure Exercise among Postmenopausal Women with Osteoarthritic Knee Pain: A Feasibility Study and Lessons Learned. Evid Based Complement Alternat Med. 2012;2012:570431. doi: 10.1155/2012/570431. PMID: 23193423.

120. Dwyer L, Parkin-Smith GF, Brantingham JW, et al. Manual and manipulative therapy in addition to rehabilitation for osteoarthritis of the knee: assessor-blind randomized pilot trial. J Manipulative Physiol Ther. 2015 Jan;38(1):1-21.e2. doi: 10.1016/j.jmpt.2014.10.002. PMID: 25455832.

121. Perlman AI, Ali A, Njike VY, et al. Massage therapy for osteoarthritis of the knee: a randomized dose-finding trial. PLoS One. 2012;7(2):e30248. doi: 10.1371/journal.pone.0030248. PMID: 22347369.

122. Atkins DV, Eichler DA. The effects of self-massage on osteoarthritis of the knee: a randomized, controlled trial. Int J Ther Massage Bodywork. 2013;6(1):4-14. PMID: 23482239.

123. Ghroubi S, Elleuch H, Kaffel N, et al. [Contribution of exercise and diet in the management of knee osteoarthritis in the obese]. Annales de réadaptation et de médecine physique : revue scientifique de la Société française de rééducation fonctionnelle de réadaptation et de médecine physique; 2008. p. 663-70.

124. Miller GD, Nicklas BJ, Davis C, et al. Intensive weight loss program improves physical function in older obese adults with knee osteoarthritis. Obesity (Silver Spring). 2006 Jul;14(7):1219-30. doi: 10.1038/oby.2006.139. PMID: 16899803.

125. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. Jama. 2013 Sep 25;310(12):1263-73. doi: 10.1001/jama.2013.277669. PMID: 24065013.

126. Bliddal H, Leeds AR, Stigsgaard L, et al. Weight loss as treatment for knee osteoarthritis symptoms in obese patients: 1-year results from a randomised controlled trial. Ann Rheum Dis. 2011 Oct;70(10):1798-803. doi: 10.1136/ard.2010.142018. PMID: 21821622.

127. Somers TJ, Blumenthal JA, Guilak F, et al. Pain coping skills training and lifestyle behavioral weight management in patients with knee osteoarthritis: a randomized controlled study. Pain. 2012 Jun;153(6):1199-209. doi: 10.1016/j.pain.2012.02.023. PMID: 22503223.

128. Atukorala I, Makovey J, Lawler L, et al. Is there a dose response relationship between weight loss and symptom improvement in persons with knee osteoarthritis? Arthritis Care & Research. 2016;[Epub ahead of print]doi: DOI 10.1002/acr.22805.

129. Makovey J, Lawler L, Bennell KL, et al. Dose response relationship between weight loss and improvement in quality of life in persons with symptomatic knee osteoarthritis. Osteoarthritis and Cartilage. 2015 April;23 SUPPL. 2:A386.

130. Claes BEA, Leung HWC, Matters K, et al. Interim analysis: An interdisciplinary team approach in facilitating weight reduction and improving function for people with knee or hip osteoarthritis. The Osteoarthritis Chronic Care Program at Royal North Shore Hospital. Nutrition & Dietetics. 2015 Sep;72(3):232-9. PMID: WOS:000362590300006.

131. Richette P, Poitou C, Garnero P, et al. Benefits of massive weight loss on symptoms, systemic inflammation and cartilage turnover in obese patients with knee osteoarthritis. Ann Rheum Dis. 2011 Jan;70(1):139-44. doi: 10.1136/ard.2010.134015. PMID: 20980288.

132. Stefanik J, Felson DT, Niu J, et al. The Relation of Massive Weight Loss to Changes in Knee Pain and Sensitization [abstract]. 2015 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2015;67 (suppl 10):3251.

133. Coleman S, Briffa NK, Carroll G, et al. A randomised controlled trial of a self-management education program for osteoarthritis of the knee delivered by health care professionals. Arthritis Res Ther. 2012;14(1):R21. doi: 10.1186/ar3703. PMID: 22284848.

134. Hochberg MC, Clegg DO. Potential effects of chondroitin sulfate on joint swelling: a GAIT report. Osteoarthritis Cartilage. 2008;16 Suppl 3:S22-4. doi: 10.1016/j.joca.2008.06.024. PMID: 18768335.

135. Messier SP, Mihalko SL, Beavers DP, et al. Strength training for arthritis trial (START): Design and rationale. BMC Musculoskeletal Disorders. 2013;14(208) PMID: 2013479802 MEDLINE PMID 23855596 (http://www.ncbi.nlm.nih.gov/pubmed/23855596) FULL TEXT LINK http://dx.doi.org/10.1186/1471-2474-14-208.

136. Kan L, Zhang J, Yang Y, et al. The Effects of Yoga on Pain, Mobility, and Quality of Life in Patients with Knee Osteoarthritis: A Systematic Review. Evid Based Complement

Alternat Med. 2016;2016:6016532. doi: 10.1155/2016/6016532. PMID: 27777597.

137. Duivenvoorden T, Brouwer Reinoud W, van Raaij Tom M, et al. Braces and orthoses for treating osteoarthritis of the knee. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2015.

138. Anwer S, Alghadir A, Brismee JM. Effect of Home Exercise Program in Patients With Knee Osteoarthritis: A Systematic Review and Meta-analysis. J Geriatr Phys Ther. 2016 Jan-Mar;39(1):38-48. doi: 10.1519/jpt.0000000000000045. PMID: 25695471.

139. Button K, Roos PE, Spasic I, et al. The clinical effectiveness of self-care interventions with an exercise component to manage knee conditions: A systematic review. Knee. 2015 Oct;22(5):360-71. PMID: WOS:000365063300002.

140. Regnaux JP, Lefevre-Colau MM, Trinquart L, et al. High-intensity versus low-intensity physical activity or exercise in people with hip or knee osteoarthritis. Cochrane Database Syst Rev. 2015;10:Cd010203. doi: 10.1002/14651858.CD010203.pub2. PMID: 26513223.

141. Tubach F, Ravaud P, Martin-Mola E, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: Results from a prospective multinational study. Arthritis Care Res (Hoboken). 2012 Nov;64(11):1699-707. doi: 10.1002/acr.21747. PMID: 22674853.

142. McAlindon TE, Driban JB, Henrotin Y, et al. OARSI Clinical Trials Recommendations: Design, conduct, and reporting of clinical trials for knee osteoarthritis. Osteoarthritis Cartilage. 2015 May;23(5):747-60. doi: 10.1016/j.joca.2015.03.005. PMID: 25952346.

143. Cho JJ, Kim TW, Park YM, et al. Tissuegene-C (InvossaTM) in patients with osteoarthritis: A phase II trials. Cytotherapy. 2015 June;17(6 SUPPL. 1):S84.

144. Cho J, Kim T, Park Y, et al. Tissuegene-C (Invossa™) in patients with osteoarthritis: A phase II trials. Osteoarthritis and Cartilage. 2015 April;23 SUPPL. 2:A170.

145. Lee B, Cho J, Kim T, et al. Tissuegene-C (TG-C), TGF-β1 transduced chondrocyte, improved clinical scores in patients with osteoarthritis: A phase 2B study. Molecular Therapy. 2014 June;22 SUPPL. 1:S292-S3.

146. Ha CW, Cho JJ, Elmallah RK, et al. A Multicenter, Single-Blind, Phase IIa Clinical Trial to Evaluate the Efficacy and Safety of a Cell-Mediated Gene Therapy in Degenerative Knee Arthritis Patients. Hum Gene Ther Clin Dev. 2015 Jun;26(2):125-30. doi: 10.1089/humc.2014.145. PMID: 25760423.

147. Messier SP, Callahan LF, Golightly YM, et al. OARSI Clinical Trials Recommendations: Design and conduct of clinical trials of lifestyle diet and exercise interventions for osteoarthritis. Osteoarthritis and Cartilage. 2015 May;23(5):787-97. PMID: WOS:000353821200011.

148. Fitzgerald GK, Hinman RS, Zeni J, Jr., et al. OARSI Clinical Trials Recommendations: Design and conduct of clinical trials of rehabilitation interventions for osteoarthritis. Osteoarthritis Cartilage. 2015 May;23(5):803-14. doi: 10.1016/j.joca.2015.03.013. PMID: 25952351.

Abbreviations/Acronyms

AAOS	American Academy of Orthopaedic Surgeons
ACR	American College of Rheumatology
ADL	Activities of Daily Living
AHRQ	Agency for Healthcare Research and Quality
BWM	behavioral weight management
CI	confidence intervals
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
HRQoL	Health-related Quality of Life
K-L	Kellgren-Lawrence
MCID	minimum clinically important difference
MCII	minimum clinically important improvement;
MD	mean difference
MRI	Magnetic resonance imaging
N/A	not applicable
NMES	neuromuscular electrical stimulation
N/R	not reported
NRS	Numeric Rating Scale
PCST	pain coping skills training
PEMF	Pulsed Electromagnetic Field Therapy
PICOT	Participants, interventions, comparators, outcomes, timing
PRP	Platelet-rich Plasma
QoL	quality of life
RCT	randomized controlled trial
RoB	risk of bias
SF	short form
SMD	standardized mean difference
SoE	strength of evidence
ST	strength training

TENS	transcutaneous electrical nerve stimulation
TUG	timed up and go
U/S	Ultrasound
VAS	visual analog scale
WBV	whole-body vibration
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Appendix A. Search Strategy

SEARCHES RUN IN JULY/AUGUST 2015 [For Surveillance]

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 1/1/2006-7/10/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:

GLUCOSAMINE:
“osteoarthritis, knee"[MH] OR ("osteoarthritis"[MH] AND (knee[tiab] OR knees[tiab])) OR (osteoarthritis*[tiab] AND (knee[tiab] OR knees[tiab])) OR ("osteoarthritis"[MH] AND (patellofemoral[tiab] OR patello-femoral[tiab])
AND
Glucosamine[MH] OR "Chondroitin"[MH] OR glucosamine OR acetylglucosamine OR "n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin

NEW THERAPIES:
“osteoarthritis, knee"[MH] OR ("osteoarthritis"[MH] AND (knee[tiab] OR knees[tiab])) OR (osteoarthritis*[tiab] AND (knee[tiab] OR knees[tiab])) OR ("osteoarthritis"[MH] AND (patellofemoral[tiab] OR patello-femoral[tiab])
AND
monovisc OR duloxetine* OR cymbalta OR selective serotonin* OR ssnri OR milnacipran OR savella OR venlafaxine OR effexor OR desvenlafaxine OR pristiq OR "il-1" OR interleukin* OR anakinra OR canakinumab OR "platelet rich plasma" OR "platelet-rich plasma" OR PRP OR "nerve growth factor" OR fibroblast growth OR shoe wedge* OR capsaicin

MANUALLY SEARCHED ENDNOTE TO FILTER ABOVE RESULTS FOR THE FOLLOWING TERMS REPRESENTING STUDY DESIGNS:
Comparative
Evaluation
Follow-up
Follow up
Prospective
Placebo
Clinical trial
Mask
Single-blind
Double-blind
Blind
Random
RCT
Research design
Control

Volunteer
Systematic review
Meta-analy*
Meta analy*
Metaanaly*
Database or Data base
Case series (for Arthroscopy only)

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 1/1/2006-7/21/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:

GLUCOSAMINE:
'knee osteoarthritis'/exp OR 'knee osteoarthritis' OR ('osteoarthritis'/exp OR osteoarthritis AND ('knee'/exp OR knee OR knees OR patellofemoral OR 'patello femoral'))
AND
'chondroitin' OR 'chondroitin'/exp OR chondroitin OR 'glucosamine' OR 'glucosamine'/exp OR glucosamine OR 'acetylglucosamine' OR 'acetylglucosamine'/exp OR acetylglucosamine OR 'n-acetylglucosamine'/exp OR 'n-acetylglucosamine' OR 'n-acetyl-d-glucosamine'/exp OR 'n-acetyl-d-glucosamine'
AND
Human/de

NEW THERAPIES:
'knee osteoarthritis'/exp OR 'knee osteoarthritis' OR ('osteoarthritis'/exp OR osteoarthritis AND ('knee'/exp OR knee OR knees OR patellofemoral OR 'patello femoral'))
AND
'monovisc' OR 'monovisc'/exp OR monovisc OR duloxetine* OR 'cymbalta' OR 'cymbalta'/exp OR cymbalta OR (selective AND serotonin*) OR 'ssnri' OR 'ssnri'/exp OR ssnri OR 'milnacipran' OR 'milnacipran'/exp OR milnacipran OR 'savella' OR 'savella'/exp OR savella OR 'venlafaxine' OR 'venlafaxine'/exp OR venlafaxine OR 'effexor' OR 'effexor'/exp OR effexor OR 'desvenlafaxine' OR 'desvenlafaxine'/exp OR desvenlafaxine OR 'pristiq' OR 'pristiq'/exp OR pristiq OR 'il-1'/exp OR 'il-1' OR interleukin* OR 'anakinra' OR 'anakinra'/exp OR anakinra OR 'canakinumab' OR 'canakinumab'/exp OR canakinumab OR 'platelet rich plasma'/exp OR 'platelet rich plasma' OR 'platelet-rich plasma'/exp OR 'platelet-rich plasma' OR 'prp' OR 'prp'/exp OR prp OR 'nerve growth factor'/exp OR 'nerve growth factor' OR (('fibroblast' OR 'fibroblast'/exp OR fibroblast) AND ('growth' OR 'growth'/exp OR growth)) OR (('shoe' OR 'shoe'/exp OR shoe) AND wedge*) OR capsaicin*
AND
Human/de

MANUALLY SEARCHED ENDNOTE TO FILTER ABOVE RESULTS FOR THE FOLLOWING TERMS REPRESENTING STUDY DESIGNS:
Comparative

Follow-up
Follow up
Prospective
Placebo
Trial
Mask
Single-blind
Double-blind
Blind
Random
RCT
Research design
Control
Volunteer
Systematic review
Meta-analy*
Meta analy*
Database or Data base
Case series (for Arthroscopy only)

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
Cochrane Databases of Systematic Reviews, Other Reviews, CENTRAL, Methods, Technology Assessment, Economic Evaluations – 1/1/2006-8/3/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:

GLUCOSAMINE:
osteoarthritis and (knee or knees or patellofemoral or patello-femoral):ti,ab,kw
AND
glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin:ti,ab,kw

NEW THERAPIES:
osteoarthritis and (knee or knees or patellofemoral or patello-femoral):ti,ab,kw
AND
monovisc or duloxetine* or cymbalta or selective serotonin* or ssnri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge* or capsaicin:ti,ab,kw

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
International Pharmaceutical Abstracts – 1/1/2006-8/4/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:

GLUCOSAMINE:
ab(osteoarthritis and (knee or knees or patellofemoral or patello-femoral)) OR ti(osteoarthritis and (knee or knees or patellofemoral or patello-femoral)) OR su(osteoarthritis and (knee or knees or patellofemoral or patello-femoral))
AND
ab(glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin) OR ti(glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin) OR su(glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin)

NEW THERAPIES:
ab(osteoarthritis and (knee or knees or patellofemoral or patello-femoral)) OR ti(osteoarthritis and (knee or knees or patellofemoral or patello-femoral)) OR su(osteoarthritis and (knee or knees or patellofemoral or patello-femoral))
AND
ab(monovisc or duloxetine* or cymbalta or selective serotonin* or ssnri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge* or capsaicin) OR ti(monovisc or duloxetine* or cymbalta or selective serotonin* or ssnri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge* or capsaicin) OR su(monovisc or duloxetine* or cymbalta or selective serotonin* or ssnri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge* or capsaicin)

==========

UPDATES RUN IN NOVEMBER/DECEMBER 2015 for the report

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 6/1/2015-11/4/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:

GLUCOSAMINE:
"osteoarthritis, knee"[MH] OR ("osteoarthritis"[MH] AND (knee[tiab] OR knees[tiab])) OR (osteoarthritis*[tiab] AND (knee[tiab] OR knees[tiab])) OR ("osteoarthritis"[MH] AND (patellofemoral[tiab] OR patello-femoral[tiab]))
AND

Glucosamine[MH] OR "Chondroitin"[MH] OR glucosamine OR acetylglucosamine OR "n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin

NEW THERAPIES:
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 6/1/2015-12/2/2015

"osteoarthritis, knee"[MH] OR ("osteoarthritis"[MH] AND (knee[tiab] OR knees[tiab])) OR (osteoarthritis*[tiab] AND (knee[tiab] OR knees[tiab])) OR ("osteoarthritis"[MH] AND (patellofemoral[tiab] OR patello-femoral[tiab]))
AND
duloxetine* OR cymbalta OR selective serotonin* OR ssnri OR milnacipran OR savella OR venlafaxine OR effexor OR desvenlafaxine OR pristiq OR "il-1" OR interleukin* OR anakinra OR canakinumab OR "platelet rich plasma" OR "platelet-rich plasma" OR PRP OR "nerve growth factor" OR fibroblast growth OR shoe wedge* OR capsaicin

ADDITIONAL THERAPIES:

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed - 1/1/2006-12/11/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:
"osteoarthritis, knee"[MH] OR ("osteoarthritis"[MH] AND (knee[tiab] OR knees[tiab])) OR (osteoarthritis*[tiab] AND (knee[tiab] OR knees[tiab])) OR ("osteoarthritis"[MH] AND (patellofemoral[tiab] OR patello-femoral[tiab])) OR ("osteoarthritis"[tiab] AND (patellofemoral[tiab] OR patello-femoral[tiab])
AND
acupuncture[tiab] OR acupuncture[ot] OR braces OR orthotic* OR orthosis OR orthoses OR stem cell* OR physical therapy OR exercis* OR herbal supplement* OR transdermal OR topical analgesic* OR analgesic cream* OR prolotherap* OR weight loss OR losing weight OR diet OR dieting OR weight reduc* OR cell-based therap* OR "Acupuncture Therapy"[Mesh] OR "Orthotic Devices"[Mesh] OR "Stem Cells"[Mesh] OR "Physical Therapy Modalities"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR "Exercise Therapy"[Mesh] OR "Transdermal Patch"[Mesh] OR "Weight Loss"[Mesh] OR "Diet, Reducing"[Mesh] OR "Weight Reduction Programs"[Mesh] OR (dietary supplements[mh] AND (plants, medicinal[mh] OR plant extracts[mh])) OR (administration, topical[mh] AND analgesics[mh])

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 1/1/2015-11/5/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:

GLUCOSAMINE:
'knee osteoarthritis'/exp OR 'knee osteoarthritis' OR ('osteoarthritis' OR 'osteoarthritis'/exp OR osteoarthritis AND ('knee' OR 'knee'/exp OR knee OR knees OR patellofemoral OR 'patello femoral')) AND [english]/lim AND [humans]/lim AND [2015-2015]/py
AND
'chondroitin' OR 'chondroitin'/exp OR chondroitin OR 'glucosamine' OR 'glucosamine'/exp OR glucosamine OR 'acetylglucosamine' OR 'acetylglucosamine'/exp OR acetylglucosamine OR 'n-acetylglucosamine'/exp OR 'n-acetylglucosamine' OR 'n-acetyl-d-glucosamine'/exp OR 'n-acetyl-d-glucosamine'

NEW THERAPIES:

DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 1/1/2015-11/5/2015

'knee osteoarthritis'/exp OR 'knee osteoarthritis' OR ('osteoarthritis' OR 'osteoarthritis'/exp OR osteoarthritis AND ('knee' OR 'knee'/exp OR knee OR knees OR patellofemoral OR 'patello femoral'))
AND
duloxetine* OR 'cymbalta' OR 'cymbalta'/exp OR cymbalta OR (selective AND serotonin*) OR 'ssnri' OR 'ssnri'/exp OR ssnri OR 'milnacipran' OR 'milnacipran'/exp OR milnacipran OR 'savella' OR 'savella'/exp OR savella OR 'venlafaxine' OR 'venlafaxine'/exp OR venlafaxine OR 'effexor' OR 'effexor'/exp OR effexor OR 'desvenlafaxine' OR 'desvenlafaxine'/exp OR desvenlafaxine OR 'pristiq' OR 'pristiq'/exp OR pristiq OR 'il-1'/exp OR 'il-1' OR interleukin* OR 'anakinra' OR 'anakinra'/exp OR anakinra OR 'canakinumab' OR 'canakinumab'/exp OR canakinumab OR 'platelet rich plasma'/exp OR 'platelet rich plasma' OR 'platelet-rich plasma'/exp OR 'platelet-rich plasma' OR 'prp' OR 'prp'/exp OR prp OR 'nerve growth factor'/exp OR 'nerve growth factor' OR ('fibroblast' OR 'fibroblast'/exp OR fibroblast AND ('growth' OR 'growth'/exp OR growth)) OR ('shoe' OR 'shoe'/exp OR shoe AND wedge*) OR capsaicin*
AND
Human

ADDITIONAL THERAPIES:

DATABASE SEARCHED & TIME PERIOD COVERED:
Embase - 1/1/2006-12/11/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:
'knee osteoarthritis'/exp OR 'knee osteoarthritis' OR 'osteoarthritis' OR 'osteoarthritis'/exp OR osteoarthritis AND ('knee' OR 'knee'/exp OR knee OR knees OR patellofemoral OR 'patello femoral')
AND
'acupuncture' OR 'acupuncture'/exp OR acupuncture OR 'braces' OR 'braces'/exp OR braces OR orthotic* OR 'orthosis' OR 'orthosis'/exp OR orthosis OR 'orthoses' OR 'orthoses'/exp OR orthoses OR (stem AND cell*) OR (physical AND ('therapy' OR 'therapy'/exp OR therapy)) OR exercis* OR herbal AND supplement* OR 'transdermal' OR 'transdermal'/exp OR transdermal OR ('topical' OR 'topical'/exp OR topical AND analgesic*) OR ('analgesic' OR 'analgesic'/exp OR analgesic AND cream*) OR prolotherap*

OR ('weight' OR 'weight'/exp OR weight AND (loss OR losing) OR 'diet' OR 'diet'/exp OR diet OR 'dieting' OR 'dieting'/exp OR dieting OR ('weight' OR 'weight'/exp OR weight AND reduc*) OR '(cell based' AND therap*)
AND
Humans

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
Cochrane – 1/1/2015-11/5/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:

GLUCOSAMINE:
osteoarthritis and (knee or knees or patellofemoral or patello-femoral):ti,ab,kw (Word variations have been searched)
AND
glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin:ti,ab,kw (Word variations have been searched)

NEW THERAPIES:

DATABASE SEARCHED & TIME PERIOD COVERED:
Cochrane – 1/1/2015-12/2/2015

SEARCH STRATEGY:
osteoarthritis and (knee or knees or patellofemoral or patello-femoral):ti,ab,kw Publication Year from 2015 to 2015 (Word variations have been searched)
AND
duloxetine* or cymbalta or selective serotonin* or ssnri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge* or capsaicin:ti,ab,kw (Word variations have been searched)

ADDITIONAL THERAPIES:

DATABASE SEARCHED & TIME PERIOD COVERED:
Cochrane - 1/1/2006-12/11/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:
osteoarthritis and (knee or knees or patellofemoral or patello-femoral):ti,ab,kw (Word variations have been searched)
AND

acupuncture or braces or orthotic* or orthosis or orthoses or "stem cell" or "stem cells" or "physical therapy" or exercis* or "herbal supplement" or "herbal supplements" or transdermal or "topical analgesic" or "topical analgesics" or "analgesic cream" or "analgesic creams" or prolotherap* or weight or diet or dieting or "cell-based therapy" or "cell-based therapies" 143386

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
CINAHL – 1/1/2006-11/12/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:

GLUCOSAMINE:

TI (osteoarthritis AND (knee or knees or patellofemoral or patello-femoral)) OR AB (osteoarthritis AND (knee or knees or patellofemoral or patello-femoral)) OR SU (osteoarthritis AND (knee or knees or patellofemoral or patello-femoral))
AND
TI (glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin) OR AB (glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin) OR SU (glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin

NEW THERAPIES:

DATABASE SEARCHED & TIME PERIOD COVERED:
CINAHL – 1/1/2006-12/2/2015

SEARCH STRATEGY:
TI (osteoarthritis AND (knee or knees or patellofemoral or patello-femoral) OR AB (osteoarthritis AND (knee or knees or patellofemoral or patello-femoral) OR SU (osteoarthritis AND (knee or knees or patellofemoral or patello-femoral)
AND
TI (duloxetine* or cymbalta or selective serotonin* or ssnri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge* or capsaicin) OR AB (duloxetine* or cymbalta or selective serotonin* or ssnri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge* or capsaicin) OR SU (duloxetine* or cymbalta or selective serotonin* or ssnri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge* or capsaicin)

ADDITIONAL THERAPIES:

DATABASE SEARCHED & TIME PERIOD COVERED:
CINAHL - 1/1/2006-12/4/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:
TI (osteoarthritis and (knee or knees or patellofemoral or patello-femoral)) OR AB (osteoarthritis and (knee or knees or patellofemoral or patello-femoral)) OR SU (osteoarthritis and (knee or knees or patellofemoral or patello-femoral)
AND
TI (acupuncture or braces or orthotic* or orthosis or orthoses or "stem cell" or "stem cells" or "physical therapy" or exercis* or "herbal supplement" or "herbal supplements" or transdermal or "topical analgesic" or "topical analgesics" or "analgesic cream" or "analgesic creams" or prolotherap* or weight or diet or dieting or "cell-based therapy" or "cell-based therapies") OR AB (acupuncture or braces or orthotic* or orthosis or orthoses or "stem cell" or "stem cells" or "physical therapy" or exercis* or "herbal supplement" or "herbal supplements" or transdermal or "topical analgesic" or "topical analgesics" or "analgesic cream" or "analgesic creams" or prolotherap* or weight or diet or dieting or "cell-based therapy" or "cell-based therapies") OR SU (acupuncture or braces or orthotic* or orthosis or orthoses or "stem cell" or "stem cells" or "physical therapy" or exercis* or "herbal supplement" or "herbal supplements" or transdermal or "topical analgesic" or "topical analgesics" or "analgesic cream" or "analgesic creams" or prolotherap* or weight or diet or dieting or "cell-based therapy" or "cell-based therapies")

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
Web of Science – Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC 1/1/2006-12/2/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:

GLUCOSAMINE:
TOPIC: (osteoarthritis and (knee or knees or patellofemoral or patello-femoral)
AND
TOPIC: (glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin)

NEW THERAPIES:

DATABASE SEARCHED & TIME PERIOD COVERED:
Web of Science – Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC 1/1/2006-12/2/2015

SEARCH STRATEGY:
TS=(osteoarthritis and (knee or knees or patellofemoral or patello-femoral)
AND
TS=(duloxetine* or cymbalta or selective serotonin* or ssnri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge* or capsaicin)

ADDITIONAL THERAPIES:

DATABASE SEARCHED & TIME PERIOD COVERED:
Web of Science Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC - 1/1/2006-12/14/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:
ts=(osteoarthritis) AND ts=(knee or knees or patellofemoral or patello-femoral)
AND
ts=(acupuncture or braces or orthotic* or orthosis or orthoses or "stem cell" or "stem cells" or "physical therapy" or exercis* or "herbal supplement" or "herbal supplements" or transdermal or "topical analgesic" or "topical analgesics" or "analgesic cream" or "analgesic creams" or prolotherap* or weight or diet or dieting or "cell-based therapy" or "cell-based therapies")

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
Scopus - 1/1/2006-11/6/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:

GLUCOSAMINE:
TITLE-ABS-KEY (osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral))
AND
TITLE-ABS-KEY (glucosamine OR acetylglucosamine OR "n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin))
AND
SUBJAREA (mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal OR mult OR arts OR busi OR deci OR econ OR psyc OR soci)

NEW THERAPIES

DATABASE SEARCHED & TIME PERIOD COVERED:
Scopus - 1/1/2006-12/2/2015

SEARCH STRATEGY:
TITLE-ABS-KEY (osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral))
AND
SUBJAREA (mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal OR mult OR arts OR busi OR deci OR econ OR psyc OR soci)
AND
TITLE-ABS-KEY (duloxetine* OR cymbalta OR selective serotonin* OR ssnri OR milnacipran OR savella OR venlafaxine OR effexor OR desvenlafaxine OR pristiq OR "il-1" OR interleukin* OR anakinra OR canakinumab OR "platelet rich plasma" OR "platelet-rich plasma" OR prp OR ("nerve growth factor" OR fibroblast growth OR shoe wedge* OR capsaicin)
AND
SUBJAREA (mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal OR mult OR arts OR busi OR deci OR econ OR psyc OR soci)

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
International Pharmaceutical Abstracts - 6/29/2015-11/18/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGY:
ab(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)) OR ti(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)) OR su(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral))

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
AMED (Allied & Complementary Medicine) - 6/29/2015-11/18/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:

GLUCOSAMINE:
ab(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)) OR ti(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)) OR su(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral))
AND
ab(glucosamine OR acetylglucosamine OR "n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin) OR ti(glucosamine OR acetylglucosamine OR "n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin) OR su(glucosamine OR acetylglucosamine OR "n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin)

NEW THERAPIES:

DATABASE SEARCHED & TIME PERIOD COVERED:

AMED (Allied & Complementary Medicine) - 6/29/2015-11/18/2015

SEARCH STRATEGY:
ab(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)) OR ti(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)) OR su(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)
AND
ab(duloxetine* or cymbalta or selective serotonin* or ssnri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge* or capsaicin) OR ti(duloxetine* or cymbalta or selective serotonin* or ssnri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge* or capsaicin) OR su(duloxetine* or cymbalta or selective serotonin* or ssnri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge* or capsaicin)

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
ClinicalTrials.gov – 1/1/2006-11/10/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:

GLUCOSAMINE:
KEYWORD :knee OR knees OR patellofemoral OR patello-femoral
AND
CONDITION:osteoarthritis
AND
INTERVENTION: glucosamine OR acetylglucosamine OR "n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin

NEW THERAPIES:
KEYWORD:knee OR knees OR patellofemoral OR patello-femoral
AND
CONDITION:osteoarthritis
AND
INTERVENTION:duloxetine OR cymbalta OR selective serotonin OR ssnri OR milnacipran OR savella OR venlafaxine OR effexor OR desvenlafaxine OR pristiq OR "il-1" OR interleukin OR anakinra OR canakinumab OR "platelet rich plasma" OR "platelet-rich plasma" OR PRP OR "nerve growth factor" OR fibroblast growth OR shoe wedge OR shoe wedges OR capsaicin

ADDITIONAL THERAPIES:

DATABASE SEARCHED & TIME PERIOD COVERED:

ClinicalTrials.gov - 1/1/2006-12/21/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:
KEYWORD: knee OR knees OR patellofemoral OR patello-femoral
CONDITION: osteoarthritis
INTERVENTION: acupuncture OR stem cell OR stem cells OR physical therapy OR diet OR diets OR nutrition OR nutritional OR weight OR obese OR obesity OR dietary supplements OR transdermal OR patch OR plant OR plants OR exercise OR exercising OR topical analgesic OR topical analgesics OR analgesic cream OR analgesic creams OR brace OR braces OR orthotic OR orthotics OR orthosis OR orthoses OR herbal supplement OR herbal supplements OR prolotherapy or prolotherapies OR prolotherapeutic OR cell-based

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
PEDRO - 1/1/2006-12/11/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGIES:
Abstract & Title: Osteoarthritis
AND
Abstract & Title: knee

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
WHO International Clinical Trials Registry - 1/1/2006-12/15/2015

LANGUAGE:
English OR Non-English with English Abstract

SEARCH STRATEGY:
CONDITION: Osteoarthritis AND knee

UPDATE SEARCHES IN SEPTEMBER 2016 FOR THE REPORT:

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 1/1/2015-9/20/2016

LANGUAGE:
English and Non-English with English abstracts

TOPIC 1 – GLUCOSAMINE:
SEARCH STRATEGY:
"osteoarthritis, knee"[MH] OR ("osteoarthritis"[MH] AND (knee[tiab] OR knees[tiab])) OR (osteoarthritis*[tiab] AND (knee[tiab] OR knees[tiab])) OR ("osteoarthritis"[MH] AND (patellofemoral[tiab] OR patello-femoral[tiab]))
AND
Glucosamine[MH] OR "Chondroitin"[MH] OR glucosamine OR acetylglucosamine OR "n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin

TOPIC 2 – ADDITIONAL THERAPIES
SEARCH STRATEGY:
SEARCH STRATEGY:
"osteoarthritis, knee"[MH] OR ("osteoarthritis"[MH] AND (knee[tiab] OR knees[tiab])) OR (osteoarthritis*[tiab] AND (knee[tiab] OR knees[tiab])) OR ("osteoarthritis"[MH] AND (patellofemoral[tiab] OR patello-femoral[tiab]))
AND
braces OR orthotic* OR orthosis OR orthoses OR stem cell* OR physical therapy OR exercis* OR weight loss OR losing weight OR diet OR dieting OR weight reduc* OR cell-based therap* OR "Orthotic Devices"[Mesh] OR "Stem Cells"[Mesh] OR "Physical Therapy Modalities"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR "Exercise Therapy"[Mesh] OR "Weight Loss"[Mesh] OR "Diet, Reducing"[Mesh] OR "Weight Reduction Programs"[Mesh] OR dietary supplements[mh] OR (administration, topical[mh] AND analgesics[mh])

TOPIC 3 – NEW THERAPIES
SEARCH STRATEGY:
"osteoarthritis, knee"[MH] OR ("osteoarthritis"[MH] AND (knee[tiab] OR knees[tiab])) OR (osteoarthritis*[tiab] AND (knee[tiab] OR knees[tiab])) OR ("osteoarthritis"[MH] AND (patellofemoral[tiab] OR patello-femoral[tiab]))
AND
"platelet rich plasma" OR "platelet-rich plasma" OR PRP OR fibroblast growth OR shoe wedge*

DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 1/1/2015-9/20/2016

LANGUAGE:
English and Non-English with English abstracts

TOPIC 1 – GLUCOSAMINE:
SEARCH STRATEGY:

'knee osteoarthritis'/exp OR 'knee osteoarthritis' OR (('osteoarthritis' OR 'osteoarthritis'/exp OR osteoarthritis) AND ('knee' OR 'knee'/exp OR knee OR knees OR patellofemoral OR 'patello femoral'))
AND
'chondroitin' OR 'chondroitin'/exp OR chondroitin OR 'glucosamine' OR 'glucosamine'/exp OR glucosamine OR 'acetylglucosamine' OR 'acetylglucosamine'/exp OR acetylglucosamine OR 'n-acetylglucosamine'/exp OR 'n-acetylglucosamine' OR 'n-acetyl-d-glucosamine'/exp OR 'n-acetyl-d-glucosamine'
AND
[humans]/lim

TOPIC 2 – ADDITIONAL THERAPIES
SEARCH STRATEGY:
'knee osteoarthritis'/exp OR 'knee osteoarthritis' OR (('osteoarthritis' OR 'osteoarthritis'/exp OR osteoarthritis) AND ('knee' OR 'knee'/exp OR knee OR knees OR patellofemoral OR 'patello femoral'))
AND
'braces' OR 'braces'/exp OR braces OR orthotic* OR 'orthosis' OR 'orthosis'/exp OR orthosis OR 'orthoses' OR 'orthoses'/exp OR orthoses OR (stem AND cell*) OR (physical AND ('therapy' OR 'therapy'/exp OR therapy)) OR exercis* OR supplement* OR prolotherap* OR ('weight' OR 'weight'/exp OR weight AND (loss OR losing)) OR 'diet' OR 'diet'/exp OR diet OR 'dieting' OR 'dieting'/exp OR dieting OR ('weight' OR 'weight'/exp OR weight AND reduc*) OR ('cell based' AND therap*)
AND
[humans]/lim

TOPIC 3 – NEW THERAPIES
SEARCH STRATEGY:
'knee osteoarthritis'/exp OR 'knee osteoarthritis' OR (('osteoarthritis' OR 'osteoarthritis'/exp OR osteoarthritis) AND ('knee' OR 'knee'/exp OR knee OR knees OR patellofemoral OR 'patello femoral'))
AND
'platelet rich plasma'/exp OR 'platelet rich plasma' OR 'platelet-rich plasma'/exp OR 'platelet-rich plasma' OR 'prp' OR 'prp'/exp OR prp OR ('fibroblast' OR 'fibroblast'/exp OR (fibroblast AND ('growth' OR 'growth'/exp OR growth)) OR (('shoe' OR 'shoe'/exp OR shoe) AND wedge*)
AND
[humans]/lim

DATABASE SEARCHED & TIME PERIOD COVERED:
Cochrane – 1/1/2015-9/20/2016

LANGUAGE:
English and Non-English with English abstracts

TOPIC 1 – GLUCOSAMINE:
SEARCH STRATEGY:
osteoarthritis and (knee or knees or patellofemoral or patello-femoral):ti,ab,kw
AND
glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin:ti,ab,kw

TOPIC 2 – ADDITIONAL THERAPIES

SEARCH STRATEGY:
osteoarthritis and (knee or knees or patellofemoral or patello-femoral):ti,ab,kw
AND
braces or orthotic* or orthosis or orthoses or "stem cell" or "stem cells" or "physical therapy" or exercis* or prolotherap* or weight or diet or dieting or "cell-based therapy" or "cell-based therapies":ti,ab,kw

TOPIC 3 – NEW THERAPIES
SEARCH STRATEGY:
osteoarthritis and (knee or knees or patellofemoral or patello-femoral):ti,ab,kw
AND
"platelet rich plasma" or "platelet-rich plasma" or PRP or fibroblast growth or shoe wedge*:ti,ab,kw

---

DATABASE SEARCHED & TIME PERIOD COVERED:
CINAHL – 1/1/2015-9/20/2016

LANGUAGE:
English and Non-English with English abstracts

TOPIC 1 – GLUCOSAMINE:
SEARCH STRATEGY:
TI (osteoarthritis AND (knee or knees or patellofemoral or patello-femoral)) OR AB (osteoarthritis AND (knee or knees or patellofemoral or patello-femoral)) OR MW (osteoarthritis AND (knee or knees or patellofemoral or patello-femoral))
AND
TI (glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin) OR AB (glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin) OR MW (glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin)

TOPIC 2 – ADDITIONAL THERAPIES
SEARCH STRATEGY:
TI (osteoarthritis AND (knee or knees or patellofemoral or patello-femoral)) OR AB (osteoarthritis AND (knee or knees or patellofemoral or patello-femoral)) OR MW (osteoarthritis AND (knee or knees or patellofemoral or patello-femoral))
AND
TI (braces or orthotic* or orthosis or orthoses or "stem cell" or "stem cells" or "physical therapy" or exercis* or weight or diet or dieting or "cell-based therapy" or "cell-based therapies") OR AB (braces or orthotic* or orthosis or orthoses or "stem cell" or "stem cells" or "physical therapy" or exercis* or weight or diet or dieting or "cell-based therapy" or "cell-based therapies") OR MW ((braces or orthotic* or orthosis or orthoses or "stem cell" or "stem cells" or "physical therapy" or exercis* or weight or diet or dieting or "cell-based therapy" or "cell-based therapies")

TOPIC 3 – NEW THERAPIES
SEARCH STRATEGY:

TI (osteoarthritis AND (knee or knees or patellofemoral or patello-femoral)) OR AB (osteoarthritis AND (knee or knees or patellofemoral or patello-femoral)) OR MW (osteoarthritis AND (knee or knees or patellofemoral or patello-femoral))
AND
TI (platelet rich plasma" or "platelet-rich plasma" or PRP OR fibroblast growth or shoe wedge*) OR AB ("platelet rich plasma" or "platelet-rich plasma" or PRP OR fibroblast growth or shoe wedge*) OR MW ("platelet rich plasma" or "platelet-rich plasma" or PRP OR fibroblast growth or shoe wedge*)

DATABASE SEARCHED & TIME PERIOD COVERED:
Web of Science – 1/1/2015-9/20/2016

LANGUAGE:
English and Non-English with English abstracts

TOPIC 1 – GLUCOSAMINE:
SEARCH STRATEGY:
TS=(osteoarthritis and (knee or knees or patellofemoral or patello-femoral))
AND
TS=(glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin)

TOPIC 2 – ADDITIONAL THERAPIES
SEARCH STRATEGY:
TS=(osteoarthritis and (knee or knees or patellofemoral or patello-femoral))
AND
ts=(braces or orthotic* or orthosis or orthoses or "stem cell" or "stem cells" or "physical therapy" or exercis* or prolotherap* or weight or diet or dieting or "cell-based therapy" or "cell-based therapies")

TOPIC 3 – NEW THERAPIES
SEARCH STRATEGY:
TS=(osteoarthritis and (knee or knees or patellofemoral or patello-femoral))
AND
ts=("platelet rich plasma" or "platelet-rich plasma" or PRP or fibroblast growth or shoe wedge*)

DATABASE SEARCHED & TIME PERIOD COVERED:
Scopus – 1/1/2015-9/20/2016

LANGUAGE:
English and Non-English with English abstracts

TOPIC 1 – GLUCOSAMINE:
SEARCH STRATEGY:
TITLE-ABS-KEY (osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral))
AND

TITLE-ABS-KEY (glucosamine OR acetylglucosamine OR "n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin)

TOPIC 2 – ADDITIONAL THERAPIES
SEARCH STRATEGY:
TITLE-ABS-KEY (osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral))
AND
TITLE-ABS-KEY (braces OR orthotic* OR orthosis OR orthoses OR "stem cell" OR "stem cells" OR "physical therapy" OR exercis* OR weight OR diet OR dieting OR "cell-based therapy" OR "cell-based therapies" **)**

TOPIC 3 – NEW THERAPIES
SEARCH STRATEGY:
TITLE-ABS-KEY (osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral))
AND
TITLE-ABS-KEY ("platelet rich plasma" OR "platelet-rich plasma" OR prp OR fibroblast growth OR shoe wedge*)

DATABASE SEARCHED & TIME PERIOD COVERED:
International Pharmaceutical Abstracts – 1/1/2015-9/20/2016

LANGUAGE:
English and Non-English with English abstracts

SEARCH STRATEGY:
ab(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)) OR ti(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)) OR su(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral))

Include medical synonyms

DATABASE SEARCHED & TIME PERIOD COVERED:
AMED – 1/1/2015-9/20/2016

LANGUAGE:
English and Non-English with English abstracts

SEARCH STRATEGY:
ab(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)) OR ti(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)) OR su(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral))

DATABASE SEARCHED & TIME PERIOD COVERED:
ClinicalTrials.gov – 1/1/2015-9/20/2016

LANGUAGE:
English and Non-English with English abstracts

TOPIC 1 – GLUCOSAMINE:
SEARCH STRATEGY:
knee OR knees OR patellofemoral OR patello-femoral | osteoarthritis | glucosamine OR acetylglucosamine OR "n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin | Studies received from 01/01/2015 to 09/20/2016

TOPIC 3 – NEW THERAPIES:
knee OR knees OR patellofemoral OR patello-femoral | osteoarthritis | "platelet rich plasma" OR "platelet-rich plasma" OR PRP OR fibroblast growth OR shoe wedge OR shoe wedges | Studies received from 01/01/2015 to 09/20/2016

DATABASE SEARCHED & TIME PERIOD COVERED:
PEDRO – 1/1/2015-9/20/2016

LANGUAGE:
English and Non-English with English abstracts

SEARCH STRATEGY:
ABSTRACT & TITLE: osteoarthritis AND knee*

DATABASE SEARCHED & TIME PERIOD COVERED:
World Health Organization ICTR – 1/1/2015-9/20/2016

LANGUAGE:
English and Non-English with English abstracts

SEARCH STRATEGY:
TITLE: Knee
CONDITION: Osteoarthritis
DATE OF REGISTRATION – BETWEEN 2015-2016

Appendix B. List of Excluded Studies

This appendix lists all studies (publications) that were identified in our literature searches that were subsequently excluded during abstract or full-text screening.

Not Human – N = 6

1. Attur M, Al-Mussawir HE, Patel J, et al. Prostaglandin E(2) exerts catabolic effects in osteoarthritis cartilage: Evidence for signaling via the EP4 receptor. Journal of Immunology. 2008 Oct;181(7):5082-8. PMID: WOS:000259755700072.

2. Bougault C, Gosset M, Houard X, et al. Stress-Induced Cartilage Degradation Does Not Depend on the NLRP3 Inflammasome in Human Osteoarthritis and Mouse Models. Arthritis and Rheumatism. 2012 Dec;64(12):3972-81. PMID: WOS:000311706300018.

3. Calado GP, Lopes AJ, Costa Junior LM, et al. Chenopodium ambrosioides L. Reduces Synovial Inflammation and Pain in Experimental Osteoarthritis. PLoS One. 2015;10(11):e0141886. doi: 10.1371/journal.pone.0141886. PMID: 26524084.

4. Dunn SL, Wilkinson JM, Crawford A, et al. Cannabinoid WIN-55,212-2 mesylate inhibits interleukin-1 beta induced matrix metalloproteinase and tissue inhibitor of matrix metalloproteinase expression in human chondrocytes. Osteoarthritis and Cartilage. 2014 Jan;22(1):133-44. PMID: WOS:000330422000017.

5. Jayasuriya CT, Goldring MB, Terek R, et al. Matrilin-3 Induction of IL-1 receptor antagonist Is required for up-regulating collagen II and aggrecan and down-regulating ADAMTS-5 gene expression. Arthritis Research & Therapy. 2012;14(5) PMID: WOS:000315488700009.

6. van Buul GM, Koevoet WL, Kops N, et al. Platelet-rich plasma releasate inhibits inflammatory processes in osteoarthritic chondrocytes. Am J Sports Med. 2011 Nov;39(11):2362-70. doi: doi: 10.1177/0363546511419278.

Not a population of interest – N = 6

1. Edwards C, Rogers A, Lynch S, et al. The effects of bariatric surgery weight loss on knee pain in patients with osteoarthritis of the knee. Arthritis. 2012;2012:504189. doi: 10.1155/2012/504189. PMID: 23243506.

2. Edwards PK, Ackland TR, Ebert JR. Accelerated weightbearing rehabilitation after matrix-induced autologous chondrocyte implantation in the tibiofemoral joint: early clinical and radiological outcomes. Am J Sports Med. 2013 Oct;41(10):2314-24. doi: 10.1177/0363546513495637. PMID: 23880403.

3. Kim YS, Kwon OR, Choi YJ, et al. Comparative Matched-Pair Analysis of the Injection Versus Implantation of Mesenchymal Stem Cells for Knee Osteoarthritis. Am J Sports Med. 2015 Nov;43(11):2738-46. doi: 10.1177/0363546515599632. PMID: 26337418.

4. Rini C, Porter L, Somers T, et al. Automated Internet-based pain coping skills training to manage osteoarthritis pain: a randomized controlled trial. Pain; 2015. p. 837-48.

5. Soni A, Joshi A, Mudge N, et al. Supervised exercise plus acupuncture for moderate to severe knee osteoarthritis: a small randomised controlled trial. Acupunct Med. 2012 Sep;30(3):176-81. doi: 10.1136/acupmed-2012-010128. PMID: 22914302.

6. Yang PF, Li D, Zhang SM, et al. Efficacy of ultrasound in the treatment of osteoarthritis of the knee. Orthop Surg. 2011 Aug;3(3):181-7. doi: 10.1111/j.1757-7861.2011.00144.x. PMID: 22009649.

Not on OA of the knee – N = 28

1. Abbott JH, Chapple C, Pinto D, et al. Exercise therapy, manual therapy, or both, for management of osteoarthritis of the hip or knee: 2-year follow-up of a randomized clinical trial. Osteoarthritis and cartilage; 2014. p. S51.

2. Alkatan M, Baker J, Machin D, et al. Improved function and reduced pain after swimming and cycling training in patients with osteoarthritis. Journal of rheumatology; 2016. p. 666-72.

3. Allen KD, Yancy WS, Jr., Bosworth HB, et al. A Combined Patient and Provider Intervention for Management of Osteoarthritis in Veterans: A Randomized Clinical Trial. Ann Intern Med. 2015 Dec 22doi: 10.7326/M15-0378. PMID: 26720751.

4. Barandun M, Iselin LD, Santini F, et al. Generation and Characterization of Osteochondral Grafts With Human Nasal Chondrocytes. Journal of Orthopaedic Research. 2015 Aug;33(8):1111-9. PMID: WOS:000357817400001.

5. Barry BK. Acute resistance exercise and pressure pain sensitivity in knee osteoarthritis: a randomised crossover trial. Osteoarthritis and cartilage; 2014. p. 407-14.

6. Bigoni M, Sacerdote P, Turati M, et al. Acute and Late Changes in Intraarticular Cytokine Levels Following Anterior Cruciate Ligament Injury. Journal of Orthopaedic Research. 2013 Feb;31(2):315-21. PMID: WOS:000313979700020.

7. Bossen D, Veenhof C, Van Beek KE, et al. Effectiveness of a web-based physical activity intervention in patients with knee and/or hip osteoarthritis: randomized controlled trial. J Med Internet Res. 2013;15(11):e257. doi: 10.2196/jmir.2662. PMID: 24269911.

8. Crossley KM, Marino GP, Macilquham MD, et al. Can patellar tape reduce the patellar malalignment and pain associated with patellofemoral osteoarthritis? Arthritis Rheum. 2009 Dec 15;61(12):1719-25. doi: 10.1002/art.24872. PMID: 19950307.

9. Ebert JR, Smith A, Fallon M, et al. Incidence, degree, and development of graft hypertrophy 24 months after matrix-induced autologous chondrocyte implantation: association with clinical outcomes. Am J Sports Med. 2015 Sep;43(9):2208-15. doi: 10.1177/0363546515591257. PMID: 26163536.

10. Gaynor PJ, Liu P, Weller MA, et al. Comparison of safety outcomes among Caucasian, Hispanic, Black, and Asian patients in duloxetine studies of chronic painful conditions. Current Medical Research and Opinion. 2013 May;29(5):549-60. PMID: WOS:000317593000013.

11. Hale LA, Waters D, Herbison P. A randomized controlled trial to investigate the effects of water-based exercise to improve falls risk and physical function in older adults with lower-extremity osteoarthritis. Arch Phys Med Rehabil. 2012 Jan;93(1):27-34. doi: 10.1016/j.apmr.2011.08.004. PMID: 21982325.

12. Hinman RS, McCrory P, Pirotta M, et al. Acupuncture for chronic knee pain: a randomized clinical trial. Deutsche Zeitschrift Fur Akupunktur. 2015;58(2):27-9. PMID: WOS:000358086100008.

13. Hughes SL, Seymour RB, Campbell RT, et al. Fit and Strong!: Bolstering Maintenance of Physical Activity Among Older Adults With Lower-extremity Osteoarthritis. American Journal of Health Behavior. 2010;34(6):750-63. PMID: WOS:000291935900010.

14. Jimenez SC, Fernandez GR, Zurita OF, et al. [Effects of education and strength training on functional tests among older people with osteoarthritis]. Rev Med Chil. 2014 Apr;142(4):436-42. doi: 10.4067/s0034-98872014000400004. PMID: 25117033.

15. Kanzaki N, Ono Y, Shibata H, et al. Glucosamine-containing supplement improves locomotor functions in subjects with knee pain: A randomized, double-blind, placebo-controlled study. Clinical Interventions in Aging. 2015 28;10:1743-53. PMID: 2015491213 FULL TEXT LINK http://dx.doi.org/10.2147/CIA.S93077.

16. Lansdown H, Howard K, Brealey S, et al. Acupuncture for pain and osteoarthritis of the knee: a pilot study for an open parallel-arm randomised controlled trial. BMC Musculoskelet Disord. 2009;10:130. doi: 10.1186/1471-2474-10-130. PMID: 19852841.

17. Martins F, Kaster T, Schutzler L, et al. Factors influencing further acupuncture usage and a more positive outcome in patients with osteoarthritis of the knee and the hip: a 3-year follow-up of a randomized pragmatic trial. Clin J Pain. 2014 Nov;30(11):953-9. doi: 10.1097/ajp.0000000000000062. PMID: 24346625.

18. Nawaz SZ, Dhinsa B, Gallagher KR, et al. Autologous chondrocyte implantation does not prevent the need for arthroplasty in patients with pre-existing osteoarthritis. Arthroscopy - Journal of Arthroscopic and Related Surgery. 2011 October;27(10 SUPPL. 1):e170-e1.

19. Parlar S, Fadiloglu C, Argon G, et al. The effects of self-pain management on the intensity of pain and pain management methods in arthritic patients. Pain Manag Nurs. 2013 Sep;14(3):133-42. doi: 10.1016/j.pmn.2010.08.002. PMID: 23972864.

20. Pisters M, Veenhof C, Schellevis F, et al. Long-term effect of exercise therapy in patients with osteoarthritis: A randomized controlled trial comparing two different physiotherapy interventions. Physiotherapy (United Kingdom); 2011. p. eS1005.

21. Satpute A, Bhatt DL, Kashyap S, et al. Effects of Bariatric Surgery on Long-Term Quality of Life Outcomes for Obese Patients with Osteoarthritis [abstract]. . Arthritis Rheumatol. 2015;67(suppl 10).

22. Tollefsrud I, Askmann E. Effect of exercise and lifestyle interventions on an outpatient rehabilitation programme for patients with hip or knee OA. Scandinavian Journal of Rheumatology. 2014 2014;43 SUPPL. 127:78-9.

23. Tsuji T, Yoon J, Kitano N, et al. Effects of N-acetyl glucosamine and chondroitin sulfate supplementation on knee pain and self-reported knee function in middle-aged and older Japanese adults: a randomized, double-blind, placebo-controlled trial. Aging Clin Exp Res. 2015 Jul 16doi: 10.1007/s40520-015-0412-6. PMID: 26178634.

24. Veenhof C, Van den Ende CH, Dekker J, et al. Which patients with osteoarthritis of hip and/or knee benefit most from behavioral graded activity? Int J Behav Med. 2007;14(2):86-91. PMID: 17926436.

25. Villacis J, Rice TR, Bucci LR, et al. Do shrimp-allergic individuals tolerate shrimp-derived glucosamine? Clinical and Experimental Allergy. 2006 Nov;36(11):1457-61. PMID: WOS:000241734300014.

26. Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. J Stat Plann Infer. 2001;99(1):25-40.

27. White DK, Neogi T, Rejeski WJ, et al. Can an Intensive Diet and Exercise Program Prevent Knee Pain Among Overweight Adults at High Risk? Arthritis Care & Research. 2015 July;67(7):965-71.

28. Yip YB, Tam AC. An experimental study on the effectiveness of massage with aromatic ginger and orange essential oil for moderate-to-severe knee pain among the elderly in Hong Kong. Complement Ther Med. 2008 Jun;16(3):131-8. doi: 10.1016/j.ctim.2007.12.003. PMID: 18534325.

Not on treating/managing OA of the knee – N = 6

1. Bennell KL, Campbell PK, Egerton T, et al. Telephone coaching to enhance a home-based physical activity program for knee osteoarthritis: A randomised clinical trial. Arthritis Care Res (Hoboken). 2016 Apr 25doi: 10.1002/acr.22915. PMID: 27111441.

2. Catay E, Ruta S, Rosa J, et al. Ultrasound (US) Findings in Patients with Knee Pain: Sensitivity and Specificity for the Diagnosis of Knee Osteoarthritis and Development of an US Prediction Score [abstract]. 2012 ACR/ARHP Annual Meeting. Arthritis rheumatol. 2012;64 (suppl S10):S53.

3. Haxby Abbott J, Chapple C, Pinto D, et al. Exercise Therapy and/or Manual Therapy for Hip or Knee Osteoarthritis: 2-Year Follow-up of a Randomized Controlled Trial [abstract]. 2014 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2014;66 (suppl S10):S1266-7.

4. Lamas JR, Tornero-Esteban P, Garcia Fernández C, et al. A Double-Blind, Randomized, Placebo-Controlled Trial of Mesenchymal Stem Cells for the Treatment of Patients with Full-Thickness Rotator Cuff Tears [abstract]. 2015 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2015;67 (suppl 10):1411.

5. Skou ST, Rasmussen S, Simonsen O, et al. Knee Confidence as It Relates to Self-reported and Objective Correlates of Knee Osteoarthritis: A Cross-sectional Study of 220 Patients. J Orthop Sports Phys Ther. 2015 Oct;45(10):765-71. doi: 10.2519/jospt.2015.5864. PMID: 26304646.

6. White D, Neogi T, Rejeski WJ, et al. Can Knee Pain be Prevented through Diet and Exercise Among Those at High Risk? the Look Ahead Study [abstract]. 2014 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2014;66 (suppl S10):S1314-5.

Not an intervention of interest – N = 95

1. Abou-Raya S, Abou-Raya A, Helmii M. Duloxetine for the management of pain in older adults with knee osteoarthritis: randomised placebo-controlled trial. Age Ageing. 2012 Sep;41(5):646-52. doi: 10.1093/ageing/afs072. PMID: 22743149.

2. Alpayci M, Ozkan Y, Yazmalar L, et al. A randomized controlled trial on the efficacy of intermittent and continuous traction for patients with knee osteoarthritis. Clin Rehabil. 2013 Apr;27(4):347-54. doi: 10.1177/0269215512459062. PMID: 22960239.

3. Anz AW, Hackel JG, Nilssen EC, et al. Application of Biologics in the Treatment of the Rotator Cuff, Meniscus, Cartilage, and Osteoarthritis. Journal of the American Academy of Orthopaedic Surgeons. 2014 Feb;22(2):68-79. PMID: WOS:000349452200002.

4. Arden NK, Reading IC, Jordan KM, et al. A randomised controlled trial of tidal irrigation vs corticosteroid injection in knee osteoarthritis: the KIVIS Study. Osteoarthritis Cartilage. 2008 Jun;16(6):733-9. doi: 10.1016/j.joca.2007.10.011. PMID: 18077189.

5. Baltzer AWA, Moser C, Jansen SA, et al. Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. Osteoarthritis and Cartilage. 2009 Feb;17(2):152-60. PMID: WOS:000263905300002.

6. Baraf HS, Gloth FM, Barthel HR, et al. Safety and efficacy of topical diclofenac sodium gel for knee osteoarthritis in elderly and younger patients: pooled data from three randomized, double-blind, parallel-group, placebo-controlled, multicentre trials. Drugs Aging. 2011 Jan 1;28(1):27-40. doi: 10.2165/11584880-000000000-00000. PMID: 21174485.

7. Barrett T, Franke R, Cheruvu N, et al. An assessment of the efficacy and tolerability of diclofenac sodium 2% topical solution for treating osteoarthritis of the knee. Journal of Pain. 2014 April;15(4 SUPPL. 1):S97.

8. Barthel HR, Haselwood D, Longley S, 3rd, et al. Randomized controlled trial of diclofenac sodium gel in knee osteoarthritis. Semin Arthritis Rheum. 2009 Dec;39(3):203-12. doi: 10.1016/j.semarthrit.2009.09.002. PMID: 19932833.

9. Belcaro G, Dugall M, Luzzi R, et al. Meriva (R) plus Glucosamine versus Condroitin plus Glucosamine in patients with knee osteoarthritis: an observational study. European Review for Medical and Pharmacological Sciences. 2014 Dec;18(24):3959-63. PMID: WOS:000352210900035.

10. Bennell KL, Kyriakides M, Metcalf B, et al. Neuromuscular versus quadriceps strengthening exercise in patients with medial knee osteoarthritis and varus malalignment: a randomized controlled trial. Arthritis Rheumatol. 2014 Apr;66(4):950-9. doi: 10.1002/art.38317. PMID: 24757146.

11. Bodick N, Lufkin J, Willwerth C, et al. An Intra-Articular, Extended-Release Formulation of Triamcinolone Acetonide Prolongs and Amplifies Analgesic Effect in Patients with Osteoarthritis of the Knee. Journal of Bone and Joint Surgery-American Volume. 2015 Jun;97A(11):877-88. PMID: WOS:000363418100003.

12. Chappell AS, Desaiah D, Liu-Seifert H, et al. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. Pain Pract. 2011 Jan-Feb;11(1):33-41. doi: 10.1111/j.1533-2500.2010.00401.x. PMID: 20602715.

13. Chappell AS, Desaiah D, Liu-Seifert H, et al. A Double-blind, Randomized, Placebo-controlled Study of the Efficacy and Safety of Duloxetine for the Treatment of Chronic Pain Due to Osteoarthritis of the Knee. Pain Practice. 2011 Jan-Feb;11(1):33-41. PMID: WOS:000296465200004.

14. Chappell AS, Ossanna MJ, Liu-Seifert H, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. Pain. 2009 Dec;146(3):253-60. doi: 10.1016/j.pain.2009.06.024. PMID: 19625125.

15. Chen LX, Mao JJ, Fernandes S, et al. Integrating acupuncture with exercise-based physical therapy for knee osteoarthritis: a randomized controlled trial. J Clin Rheumatol. 2013 Sep;19(6):308-16. doi: 10.1097/RHU.0b013e3182a21848. PMID: 23965480.

16. Chen XY, Spaeth RB, Freeman SG, et al. The modulation effect of longitudinal acupuncture on resting state functional connectivity in knee osteoarthritis patients. Molecular Pain. 2015 Oct;11 PMID: WOS:000363742900001.

17. Cheung RKH, Leung KK, Lee KC, et al. Sequential non-traumatic femoral shaft fractures in a patient on long-term alendronate. Hong Kong Medical Journal. 2007;13(6):485-9.

18. Cho J, Kim T, Park Y, et al. Tissuegene-C (Invossa™) in patients with osteoarthritis: A phase II trials. Osteoarthritis and Cartilage. 2015 April;23 SUPPL. 2:A170.

19. Cho JJ, Kim TW, Park YM, et al. Tissuegene-C (InvossaTM) in patients with osteoarthritis: A phase II trials. Cytotherapy. 2015 June;17(6 SUPPL. 1):S84.

20. Conaghan PG, Dickson J, Bolten W, et al. A multicentre, randomized, placebo- and active-controlled trial comparing the efficacy and safety of topical ketoprofen in Transfersome gel (IDEA-033) with ketoprofen-free vehicle (TDT 064) and oral celecoxib for knee pain associated with osteoarthritis. Rheumatology (Oxford). 2013 Jul;52(7):1303-12. doi: 10.1093/rheumatology/ket133. PMID: 23542612.

21. Crossley KM, Vicenzino B, Schache AG, et al. Targeted physiotherapy treatment for patellofemoral osteoarthritis: A randomised clinical trial. Osteoarthritis and cartilage; 2014. p. S431.

22. Davalillo CAT, Vasavilbaso CT, Alvarez JMN, et al. Clinical efficacy of intra-articular injections in knee osteoarthritis: A prospective randomized study comparing hyaluronic acid and betamethasone. Open Access Rheumatology: Research and Reviews; 2015. p. 9-18.

23. De Campos GC, Rezende MU, Pailo AF, et al. Adding triamcinolone improves viscosupplementation: A randomized clinical trial knee. Clinical Orthopaedics and Related Research. 2013 February;471(2):613-20. PMID: 2013346151 MEDLINE PMID 23100188 (http://www.ncbi.nlm.nih.gov/pubmed/23100188) FULL TEXT LINK http://dx.doi.org/10.1007/s11999-012-2659-y.

24. Ding MH, Zhang H, Li Y. [A randomized controlled study on warming needle moxibustion for treatment of knee osteoarthritis]. Zhongguo zhen jiu [Chinese acupuncture & moxibustion]; 2009. p. 603-7.

25. Dumais R, Benoit C, Dumais A, et al. Effect of regenerative injection therapy on function and pain in patients with knee osteoarthritis: a randomized crossover study. Pain Med. 2012 Aug;13(8):990-9. doi: 10.1111/j.1526-4637.2012.01422.x. PMID: 22759069.

26. Erhan B, Gunduz B, Ustunel SH, et al. The Efficacy of Topical Glucosamine Sulfate-Chondroitin Sulfate in Knee Osteoarthritis Treated With Physical Therapy: A Randomized, Double-Blind, Placebo-Controlled Study. Turkiye Fiziksel Tip Ve Rehabilitasyon Dergisi-Turkish Journal of Physical Medicine and Rehabilitation. 2012 Sep;58(3):194-8. PMID: WOS:000310096200006.

27. Espinosa Cuervo G, Martinez Garcia MDC, Gonzalez Carmona B, et al. Efficacy of kots russian electroestimulation in quality of life, functional capacity, muscular force and equilibrium in knee osteoarthritis: Clinical trial. Physiotherapy (United Kingdom); 2011. p. eS319-eS20.

28. Fernandes NF, Malliah R, Stitik TP, et al. Herpes zoster following intra-articular corticosteroid injection. Acta Dermatovenerol Alp Pannonica Adriat. 2009 Mar;18(1):28-30. PMID: 19350185.

29. Fioravanti A, Bellisai B, Iacoponi F, et al. Phytothermotherapy in osteoarthritis: a randomized controlled clinical trial. J Altern Complement Med. 2011 May;17(5):407-12. doi: 10.1089/acm.2010.0294. PMID: 21563963.

30. Focht BC, Garver MJ, Devor ST, et al. Group-mediated physical activity promotion and mobility in sedentary patients with knee osteoarthritis: results from the IMPACT-pilot trial. Rehabil Res Pract. 2014 Oct;41(10):2068-77. doi: 10.1155/2014/861268 10.3899/jrheum.140054. PMID: 25179854.

31. Fortin PR, Penrod JR, Clarke AE, et al. Timing of total joint replacement affects clinical outcomes among patients with osteoarthritis of the hip or knee. Arthritis Rheum. 2002 Dec;46(12):3327-30. doi: 10.1002/art.10631. PMID: 12483739.

32. Foster NE, Thomas E, Barlas P, et al. Acupuncture as an adjunct to exercise based physiotherapy for osteoarthritis of the knee: randomised controlled trial. Bmj. 2007 Sep 1;335(7617):436. doi: 10.1136/bmj.39280.509803.BE. PMID: 17699546.

33. Frakes EP, Risser RC, Ball TD, et al. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin. 2011 Dec;27(12):2361-72. doi: 10.1185/03007995.2011.633502. PMID: 22017192.

34. Garcia-Padilla S, Duarte-Vazquez MA, Gonzalez-Romero KE, et al. Effectiveness of intra-articular injections of sodium bicarbonate and calcium gluconate in the treatment of osteoarthritis of the knee: a randomized double-blind clinical trial. Bmc Musculoskeletal Disorders. 2015 May;16 PMID: WOS:000354927100001.

35. Guler O, Mutlu S, Isyar M, et al. Comparison of short-term results of intraarticular platelet-rich plasma (PRP) and hyaluronic acid treatments in early-stage gonarthrosis patients. European Journal of Orthopaedic Surgery and Traumatology. 2015 2015;25(3):509-13. PMID: 2014733485 FULL TEXT LINK http://dx.doi.org/10.1007/s00590-014-1517-x.

36. Ha CW, Cho JJ, Elmallah RK, et al. A Multicenter, Single-Blind, Phase IIa Clinical Trial to Evaluate the Efficacy and Safety of a Cell-Mediated Gene Therapy in Degenerative Knee Arthritis Patients. Hum Gene Ther Clin Dev. 2015 Jun;26(2):125-30. doi: 10.1089/humc.2014.145. PMID: 25760423.

37. Hammad Y, Magid H, Sobhy M. Clinical and biochemical study of the comparative efficacy of topical versus oral glucosamine/chondroitin sulfate on osteoarthritis of the knee. Egyptian Rheumatologist; 2015. p. 85-91.

38. Henriksen M, Christensen R, Klokker L, et al. Evaluation of the benefit of corticosteroid injection before exercise therapy in patients with osteoarthritis of the knee: a randomized clinical trial. JAMA Intern Med. 2015 Jun;175(6):923-30. doi: 10.1001/jamainternmed.2015.0461. PMID: 25822572.

39. Hochberg MC, Wohlreich M, Gaynor P, et al. Clinically relevant outcomes based on analysis of pooled data from 2 trials of duloxetine in patients with knee osteoarthritis. J Rheumatol. 2012 Feb;39(2):352-8. doi: 10.3899/jrheum.110307. PMID: 22133624.

40. Horng HC, Kuo CP, Cherng CH, et al. The effects of collateral meridian therapy for knee osteoarthritis pain management: a pilot study. J Manipulative Physiol Ther. 2013 Jan;36(1):51-6. doi: 10.1016/j.jmpt.2012.12.003. PMID: 23380214.

41. Housman L, Arden N, Schnitzer TJ, et al. Intra-articular hylastan versus steroid for knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc. 2014 Jul;22(7):1684-92. doi: 10.1007/s00167-013-2438-7. PMID: 23417236.

42. Itoh K, Hirota S, Katsumi Y, et al. Trigger point acupuncture for treatment of knee osteoarthritis--a preliminary RCT for a pragmatic trial. Acupunct Med. 2008 Mar;26(1):17-26. PMID: 18356795.

43. Jevtic T, Mejdi Z, Vukomanovic J, et al. Application of methylprednisolone suspension by iontophoresis in patients with arthrosis of the knee. Serbian Journal of Experimental and Clinical Research. 2008 2008;9(1):13-7. PMID: 2009145662.

44. Jubb RW, Tukmachi ES, Jones PW, et al. A blinded randomised trial of acupuncture (manual and electroacupuncture) compared with a non-penetrating sham for the symptoms of osteoarthritis of the knee. Acupunct Med. 2008 Jun;26(2):69-78. PMID: 18591906.

45. Kanzaki N, Saito K, Maeda A, et al. Effect of a dietary supplement containing glucosamine hydrochloride, chondroitin sulfate and quercetin glycosides on symptomatic knee

osteoarthritis: a randomized, double-blind, placebo-controlled study. J Sci Food Agric. 2012 Mar 15;92(4):862-9. doi: 10.1002/jsfa.4660. PMID: 21969261.

46. Karagulle M, Karagulle MZ, Karagulle O, et al. A 10-day course of SPA therapy is beneficial for people with severe knee osteoarthritis. A 24-week randomised, controlled pilot study. Clin Rheumatol. 2007 Dec;26(12):2063-71. doi: 10.1007/s10067-007-0618-x. PMID: 17431728.

47. Kaya E, Kaplan C, Carli AB, et al. Effects of Balneotherapy and Physical Therapy on Sleep Quality in Patients With Osteoarthritis Aged 50 to 85 Years. Archives of Rheumatology. 2016;31(1):1-5. doi: 10.5606/ArchRheumatol.2016.4625. PMID: WOS:000372922300001.

48. Kivitz A, Fairfax M, Sheldon EA, et al. Comparison of the effectiveness and tolerability of lidocaine patch 5% versus celecoxib for osteoarthritis-related knee pain: post hoc analysis of a 12 week, prospective, randomized, active-controlled, open-label, parallel-group trial in adults. Clin Ther. 2008 Dec;30(12):2366-77. doi: 10.1016/j.clinthera.2008.12.015. PMID: 19167595.

49. Kosuwon W, Sirichatiwapee W, Wisanuyotin T, et al. Efficacy of symptomatic control of knee osteoarthritis with 0.0125% of capsaicin versus placebo. J Med Assoc Thai. 2010 Oct;93(10):1188-95. PMID: 20973322.

50. Lapshina S, Myasoutova L, Afanasyeva M, et al. Comparative effectiveness of local transdermal therapy with glyukozaminosulfatis (Hondroksid Maximum) and injectable form of glyukozaminosulfatis (DONA) in patients with knee OA. Osteoporosis International. 2015 February;26(1 SUPPL. 1):S334-S5.

51. Lee B, Cho J, Kim T, et al. Tissuegene-C (TG-C), TGF-β1 transduced chondrocyte, improved clinical scores in patients with osteoarthritis: A phase 2B study. Molecular Therapy. 2014 June;22 SUPPL. 1:S292-S3.

52. Lev-Ari S, Miller E, Maimon Y, et al. Delayed effect of acupuncture treatment in OA of the knee: A blinded, randomized, controlled trial. Evidence based Complementary and Alternative Medicine. 2011;792975(410) PMID: 2011059305 FULL TEXT LINK http://dx.doi.org/10.1093/ecam/nen080.

53. Liu K, Tian LF. [Knee osteoarthritis treated with acupuncture at Neiguan (PC 6) and Taichong (LR 3)]. Zhongguo Zhen Jiu. 2013 Feb;33(2):105-8. PMID: 23620932.

54. Liu MR, Li L, He ZW. [Efficacy observation on osteoarthritis of the knee treated with the ultrastructural acupotomy therapy at the counter-Ashi points]. [Chinese]. Zhongguo zhen jiu [Chinese acupuncture & moxibustion]; 2012. p. 621-4.

55. Liu YS, Xue LG, Ma XJ, et al. Observation on pain release by long-round needle therapy in knee osteoarthritis related with meridian-sinews theory. Evidence-based Complementary and Alternative Medicine; 2013.

56. Magrans-Courtney T, Wilborn C, Rasmussen C, et al. Effects of diet type andFsupplementation of glucosamine, chondroitin, and MSM on body composition, functional status, and markers of health in women with knee osteoarthritis initiating a resistance-based exercise and weight loss program. J Int Soc Sports Nutr. 2011;8(1):8. doi: 10.1186/1550-2783-8-8. PMID: 21689421.

57. Manheimer E, Lim B, Lao L, et al. Acupuncture for knee osteoarthritis--a randomised trial using a novel sham. Acupunct Med. 2006 Dec;24 Suppl:S7-14. PMID: 17308513.

58. Mavrommatis CI, Argyra E, Vadalouka A, et al. Acupuncture as an adjunctive therapy to pharmacological treatment in patients with chronic pain due to osteoarthritis of the knee: a 3-armed, randomized, placebo-controlled trial. Pain. 2012 Aug;153(8):1720-6. doi: 10.1016/j.pain.2012.05.005. PMID: 22727499.

59. Meng CR, Fan L, Fu WB, et al. Clinical research on abdominal acupuncture plus conventional acupuncture for knee osteoarthritis. J Tradit Chin Med. 2009 Dec;29(4):249-52. PMID: 20112481.

60. Miller E, Maimon Y, Rosenblatt Y, et al. Delayed Effect of Acupuncture Treatment in OA of the Knee: A Blinded, Randomized, Controlled Trial. Evidence-Based Complementary and Alternative Medicine. 2011:1-5. PMID: WOS:000293563800001.

61. Miori R, Paolazzi G, Albertazzi R, et al. [Phytothermotherapy with fermenting alpine grass in knee osteoarthritis: mid-long term results]. Reumatismo. 2008 Oct-Dec;60(4):282-9. PMID: 19132153.

62. Moller I, Cid M, Chetrit C, et al. Effect of a topical cream containing mucopolysaccharides on knee function and pain intensity of patients with osteoarthritis. Osteoarthritis and Cartilage. 2013 April;21 SUPPL. 1:S287.

63. Nejati P, Farzinmehr A, Moradi-Lakeh M. The effect of exercise therapy on knee osteoarthritis: a randomized clinical trial. Med J Islam Repub Iran. 2015;29:186. PMID: 26034739.

64. Park SH, Park CY, Kim SK, et al. Safety and efficacy of piroxicam patches for treating knee osteoarthritis. Korean Journal of Medicine; 2008. p. 537-45.

65. Peniston JH, Gold MS, Wieman MS, et al. Long-term tolerability of topical diclofenac sodium 1% gel for osteoarthritis in seniors and patients with comorbidities. Clin Interv Aging. 2012;7:517-23. doi: 10.2147/cia.s35416. PMID: 23204844.

66. Qiu L, Kan JW, Zheng X, et al. [Observation on the long-term efficacy of knee osteoarthritis treated with warm needling and rehabilitation training]. [Chinese]. Zhongguo zhen jiu [Chinese acupuncture & moxibustion]; 2013. p. 199-202.

67. Rabago D, Kijowski R, Woods M, et al. Association between disease-specific quality of life and magnetic resonance imaging outcomes in a clinical trial of prolotherapy for knee osteoarthritis. Arch Phys Med Rehabil. 2013 Nov;94(11):2075-82. doi: 10.1016/j.apmr.2013.06.025. PMID: 23850615.

68. Rabago D, Patterson JJ, Mundt M, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. Ann Fam Med. 2013 May-Jun;11(3):229-37. doi: 10.1370/afm.1504. PMID: 23690322.

69. Ren X, Yao C, Wu F, et al. Effectiveness of moxibustion treatment in quality of life in patients with knee osteoarthritis: A randomized, double-blinded, placebo-controlled trial. Evidence-based Complementary and Alternative Medicine; 2015.

70. Ren XM, Cao JJ, Shen XY, et al. [Knee osteoarthritis treated with moxibustion: a randomized controlled trial]. Zhongguo Zhen Jiu. 2011 Dec;31(12):1057-61. PMID: 22256633.

71. Ren XM, Cao JJ, Shen XY, et al. Preliminary clinical randomized controlled trial on knee osteoarthritis treated with moxibustion. World Journal of Acupuncture - Moxibustion; 2012. p. 28-33.

72. Rossi MD, Eberle T, Roche M, et al. Delaying knee replacement and implications on early postoperative outcomes: a pilot study. Orthopedics. 2009 Dec;32(12):885. doi: 10.3928/01477447-20091020-06. PMID: 19968215.

73. Rother M, Conaghan PG. A randomized, double-blind, phase III trial in moderate osteoarthritis knee pain comparing topical ketoprofen gel with ketoprofen-free gel. J Rheumatol. 2013 Oct;40(10):1742-8. doi: 10.3899/jrheum.130192. PMID: 23996292.

74. Saleki M, Ahadi T, Razi M, et al. Comparison of the effects of acupuncture and isometric exercises on symptom of knee osteoarthritis. Int J Prev Med. 2013 Apr;4(Suppl 1):S73-7. PMID: 23717775.

75. Scharf HP, Mansmann U, Streitberger K, et al. Acupuncture and knee osteoarthritis: a three-armed randomized trial. Ann Intern Med. 2006 Jul 4;145(1):12-20. PMID: 16818924.

76. Schnitzer TJ, Pelletier JP, Haselwood DM, et al. Civamide cream 0.075% in patients with osteoarthritis of the knee: a 12-week randomized controlled clinical trial with a longterm extension. J Rheumatol. 2012 Mar;39(3):610-20. doi: 10.3899/jrheum.110192. PMID: 22089461.

77. Schnitzer TJ, Pelletier J-P, Haselwood DM, et al. Civamide cream 0 075% in patients with osteoarthritis of the knee: a 12-week randomized controlled clinical trial with a longterm extension. Journal of Rheumatology. 2012;39(3) PMID: 108170486.

78. Selvan T, Rajiah K, Nainar MSM, et al. A Clinical Study on Glucosamine Sulfate versus Combination of Glucosamine Sulfate and NSAIDs in Mild to Moderate Knee Osteoarthritis. Scientific World Journal. 2012:1-5. PMID: WOS:000303008800001.

79. Skou ST, Roos EM, Simonsen O, et al. The efficacy of non-surgical treatment on pain and sensitization in patients with knee osteoarthritis: a pre-defined ancillary analysis from a randomized controlled trial. Osteoarthritis Cartilage. 2015 Aug 1doi: 10.1016/j.joca.2015.07.013. PMID: 26241775.

80. Spaeth RB, Camhi S, Hashmi JA, et al. A longitudinal study of the reliability of acupuncture deqi sensations in knee osteoarthritis. Evid Based Complement Alternat Med. 2013;2013:204259. doi: 10.1155/2013/204259. PMID: 23935656.

81. Stutz-Doyle C. The effects of traditional strengthening exercises versus functional task training on pain, strength, and functional mobility in the 45--65 year old adult with knee osteoarthritis. Seton Hall University. 2011 PMID: 109857766.

82. Suarez-Almazor ME, Looney C, Liu Y, et al. A randomized controlled trial of acupuncture for osteoarthritis of the knee: effects of patient-provider communication. Arthritis Care Res (Hoboken). 2010 Sep;62(9):1229-36. doi: 10.1002/acr.20225. PMID: 20506122.

83. Sun K, Bao XM, Song YC, et al. [Clinical study on the treatment of knee osteoarthritis by acupuncture plus manipulative regulation of knee muscle]. Zhongguo Gu Shang. 2010 Dec;23(12):895-8. PMID: 21265192.

84. Taechaarpornkul W, Suvapan D, Theppanom C, et al. Comparison of the effectiveness of six and two acupuncture point regimens in osteoarthritis of the knee: a randomised trial. Acupunct Med. 2009 Mar;27(1):3-8. doi: 10.1136/aim.2008.000067. PMID: 19369186.

85. Tunay VB, Baltaci G, Atay AO. Hospital-based versus home-based proprioceptive and strengthening exercise programs in knee osteoarthritis. Acta Orthop Traumatol Turc. 2010;44(4):270-7. doi: 10.3944/aott.2010.2306. PMID: 21252603.

86. Vas J, Mendez C, Perea-Milla E. Acupuncture versus Streitberger needle in knee osteoarthritis -- an RCT. Acupuncture Medicine; 2006. p. S15-s24.

87. Vermesan D, Prejbeanu R, Laitin S, et al. Arthroscopic debridement compared to intra-articular steroids in treating degenerative medial meniscal tears. Eur Rev Med Pharmacol Sci. 2013 Dec;17(23):3192-6. PMID: 24338461.

88. Wang JG, He LJ. [Observation on the therapeutic effect of warming needle moxibustion on knee osteoarthritis]. Zhongguo zhen jiu [Chinese acupuncture & moxibustion]; 2007. p. 191-2.

89. Weiner DK, Moore CG, Morone NE, et al. Efficacy of periosteal stimulation for chronic pain associated with advanced knee osteoarthritis: a randomized, controlled clinical trial. Clin Ther. 2013 Nov;35(11):1703-20.e5. doi: 10.1016/j.clinthera.2013.09.025. PMID: 24184053.

90. Wi SY, Kang JH, Jang JH. Clinical Feasibility of Exercise Game for Depression Treatment in Older Women with Osteoarthritis: a Pilot Study. Journal of Physical Therapy Science. 2013 Feb;25(2):165-7. PMID: WOS:000319494300006.

91. Williamson OD, Schroer M, Ruff DD, et al. Onset of response with duloxetine treatment in patients with osteoarthritis knee pain and chronic low back pain: a post hoc analysis of placebo-controlled trials. Clin Ther. 2014 Apr 1;36(4):544-51. doi: 10.1016/j.clinthera.2014.02.009. PMID: 24650448.

92. Wu ZH, Bao F. [Observation on therapeutic effects of electroacupuncture for the treatment of knee osteoarthritis]. Zhongguo gu shang [China journal of orthopaedics and traumatology]; 2008. p. 170-2.

93. Yang XC, He SF, Wang RC, et al. [Observation on curative effect of thermal acupuncture needle muscular stimulation therapy for knee osteoarthritis patients]. Zhen Ci Yan Jiu. 2012 Jun;37(3):237-41. PMID: 22934397.

94. Zane AJ, Huang J, Bettadahalli S, et al. Hyponatremia: A complication of intra-articular corticosteroid injection. Journal of General Internal Medicine. 2013 June;28 SUPPL. 1:S343.

95. Zhao L, Cheng K, Wang L, et al. Effectiveness of moxibustion treatment as adjunctive therapy in osteoarthritis of the knee: a randomized, double-blinded, placebo-controlled clinical trial. Arthritis Res Ther. 2014;16(3):R133. doi: 10.1007/s11999-014-3743-2 10.1186/ar4590. PMID: 24962039.

Specific interventions with a sample size less than 50 – N = 32

1. Aaboe J, Henriksen M, Bartholdy C, et al. The effect of quadriceps-strengthening exercise on quadriceps and knee biomichanics during walking in adults with knee osteoarthritis: A randomized controlled trial. Osteoarthritis and cartilage; 2014. p. S80-s1.

2. Anwer S, Alghadir A. Effect of isometric quadriceps exercise on muscle strength, pain, and function in patients with knee osteoarthritis: a randomized controlled study. J Phys Ther Sci. 2014 May;26(5):745-8. doi: 10.1589/jpts.26.745. PMID: 24926143.

3. Armagan O, Yilmazer S, Calısir C, et al. Comparison of the symptomatic and chondroprotective effects of glucosamine sulphate and exercise treatments in patients with knee osteoarthritis. Journal of Back & Musculoskeletal Rehabilitation. 2015;28(2) PMID: 103782076.

4. Ay S, Koldas Dogan S, Evcik D. Is there an effective way to prescribe a home-based exercise program in patients with knee osteoarthritis? a randomized controlled study. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi; 2013. p. 1-6.

5. Bennell KL, Hunt MA, Wrigley TV, et al. Hip strengthening reduces symptoms but not knee load in people with medial knee osteoarthritis and varus malalignment: a randomised controlled trial. Osteoarthritis Cartilage. 2010 May;18(5):621-8. doi: 10.1016/j.joca.2010.01.010. PMID: 20175973.

6. Chang TF, Liou TH, Chen CH, et al. Effects of elastic-band exercise on lower-extremity function among female patients with osteoarthritis of the knee. Disabil Rehabil. 2012;34(20):1727-35. doi: 10.3109/09638288.2012.660598. PMID: 22397710.

7. Cherian JJ, Kapadia BH, Bhave A, et al. Use of Transcutaneous Electrical Nerve Stimulation Device in Early Osteoarthritis of the Knee. J Knee Surg. 2015 Aug;28(4):321-7. doi: 10.1055/s-0034-1389160. PMID: 25162407.

8. Crossley KM, Vicenzino B, Lentzos J, et al. Exercise, education, manual-therapy and taping compared to education for patellofemoral osteoarthritis: a blinded, randomised clinical trial. Osteoarthritis Cartilage. 2015 Sep;23(9):1457-64. doi: 10.1016/j.joca.2015.04.024. PMID: 25960116.

9. Durmus D, Alayli G, Aliyazicioglu Y, et al. Effects of glucosamine sulfate and exercise therapy on serum leptin levels in patients with knee osteoarthritis: preliminary results of randomized controlled clinical trial. Rheumatol Int. 2013 Mar;33(3):593-9. doi: 10.1007/s00296-012-2401-9. PMID: 22476244.

10. Durmus D, Alayli G, Bayrak IK, et al. Assessment of the effect of glucosamine sulfate and exercise on knee cartilage using magnetic resonance imaging in patients with knee osteoarthritis: a randomized controlled clinical trial. J Back Musculoskelet Rehabil. 2012;25(4):275-84. doi: 10.3233/bmr-2012-0336. PMID: 23220811.

11. Gallego-Ariza B, Mateos-Toset S, Cabrera-Martos I, et al. Impact of a supervised muscular training on perceived quality of sleep and health in a population with knee osteoarthritis. Sleep medicine; 2013. p. e63-e4.

12. Giordano N, Fioravanti A, Papakostas P, et al. The efficacy and tolerability of glucosamine sulfate in the treatment of knee osteoarthritis: A randomized, double-blind, placebo-controlled trial. Curr Ther Res Clin Exp. 2009 Jun;70(3):185-96. doi: 10.1016/j.curtheres.2009.05.004. PMID: 24683229.

13. Haflah NHM, Jaarin K, Abdullah S, et al. Palm vitamin E and glucosamine sulphate in the treatment of osteoarthritis of the knee. Saudi Medical Journal. 2009 Nov;30(11):1432-8. PMID: WOS:000273458400010.

14. Heinonen A, Multanen J, Kujala U, et al. High-impact training to improve physical performance in postmenopausal women with early osteoarthritis. Physiotherapy (United Kingdom); 2011. p. eS470-eS1.

15. Henriksen M, Klokker L, Bartholdy C, et al. The effects of exercise therapy on knee joint biomechanics during walking in patients with knee osteoarthritis: Secondary outcome analyses from a randomized controlled trial. Osteoarthritis and cartilage; 2014. p. S44.

16. Hunt MA, Keefe FJ, Bryant C, et al. A physiotherapist-delivered, combined exercise and pain coping skills training intervention for individuals with knee osteoarthritis: a pilot study. Knee. 2013 Mar;20(2):106-12. doi: 10.1016/j.knee.2012.07.008. PMID: 22921688.

17. Jorge RT, Souza MC, Chiari A, et al. Progressive resistance exercise in women with osteoarthritis of the knee: a randomized controlled trial. Clin Rehabil. 2015 Mar;29(3):234-43. doi: 10.1177/0269215514540920. PMID: 24994768.

18. Kawasaki T, Kurosawa H, Ikeda H, et al. Additive effects of glucosamine or risedronate for the treatment of osteoarthritis of the knee combined with home exercise: a prospective randomized 18-month trial. J Bone Miner Metab. 2008;26(3):279-87. doi: 10.1007/s00774-007-0813-5. PMID: 18470670.

19. Messier SP, Mihalko S, Loeser RF, et al. Glucosamine/chondroitin combined with exercise for the treatment of knee osteoarthritis: a preliminary study. Osteoarthritis Cartilage. 2007 Nov;15(11):1256-66. doi: 10.1016/j.joca.2007.04.016. PMID: 17561418.

20. Petersen SG, Beyer N, Hansen M, et al. Nonsteroidal anti-inflammatory drug or glucosamine reduced pain and improved muscle strength with resistance training in a randomized controlled trial of knee osteoarthritis patients. Arch Phys Med Rehabil. 2011 Aug;92(8):1185-93. doi: 10.1016/j.apmr.2011.03.009. PMID: 21807137.

21. Petersen SG, Beyer N, Hansen M, et al. Nonsteroidal Anti-Inflammatory Drug or Glucosamine Reduced Pain and Improved Muscle Strength With Resistance Training in a Randomized Controlled Trial of Knee Osteoarthritis Patients. Archives of Physical Medicine & Rehabilitation. 2011;92(8) PMID: 104666454.

22. Pietrosimone BG, Saliba SA, Hart JM, et al. Effects of transcutaneous electrical nerve stimulation and therapeutic exercise on quadriceps activation in people with tibiofemoral osteoarthritis. J Orthop Sports Phys Ther. 2011 Jan;41(1):4-12. doi: 10.2519/jospt.2011.3447. PMID: 21282869.

23. Railhac JJ, Zaim M, Saurel AS, et al. Effect of 12 months treatment with chondroitin sulfate on cartilage volume in knee osteoarthritis patients: a randomized, double-blind, placebo-controlled pilot study using MRI. Clin Rheumatol. 2012 Sep;31(9):1347-57. doi: 10.1007/s10067-012-2022-4. PMID: 22729470.

24. Sadeghi A, Jalili N, Asadi-Khiavi M. Low dose glucosamine and chondroitin sulfate use in knee osteoarthritis. Journal of Chemical and Pharmaceutical Research. 2014 2014;6(4):633-6. PMID: 2014314830.

25. Samuel Sundar Doss D, Rekha K, Prathap S. Effects of non weight bearing strength training for knee osteoarthritis. International Journal of Research in Pharmaceutical Sciences. 2014 30;5(3):188-92. PMID: 2015135571.

26. Samut G, Dincer F, Ozdemir O. The effect of isokinetic and aerobic exercises on serum interleukin-6 and tumor necrosis factor alpha levels, pain, and functional activity in patients with knee osteoarthritis. Mod Rheumatol. 2015 Nov;25(6):919-24. doi: 10.3109/14397595.2015.1038425. PMID: 25849853.

27. Sayers SP, Gibson K, Cook CR. Effect of high-speed power training on muscle performance, function, and pain in older adults with knee osteoarthritis: a pilot investigation. Arthritis Care Res (Hoboken). 2012 Jan;64(1):46-53. doi: 10.1002/acr.20675. PMID: 22012877.

28. Shahine EM, Elhadidi AS. Efficacy of glucosamine sulfate in lowering serum level of interleukin-1(beta) in symptomatic primary knee osteoarthritis: Clinical and laboratory study. Alexandria Journal of Medicine. 2014 June;50(2):159-63. PMID: 2014361042 FULL TEXT LINK http://dx.doi.org/10.1016/j.ajme.2014.01.006.

29. Sorour AS, Ayoub AS, Abd El Aziz EM. Effectiveness of acupressure versus isometric exercise on pain, stiffness, and physical function in knee osteoarthritis female patients. J Adv Res. 2014 Mar;5(2):193-200. doi: 10.1016/j.jare.2013.02.003. PMID: 25685487.

30. Vincent KR, Hamilton AS, Lomonaco C, et al. Progressive enhanced eccentric or concentric resistance exercise training for knee osteoarthritis: Initial results on pain and function. PM and R; 2012. p. S188.

31. Wang TJ, Lee SC, Liang SY, et al. Comparing the efficacy of aquatic exercises and land-based exercises for patients with knee osteoarthritis. J Clin Nurs. 2011 Sep;20(17-18):2609-22. doi: 10.1111/j.1365-2702.2010.03675.x. PMID: 21539629.

32. Zhang SL, Liu HQ, Xu XZ, et al. Effects of exercise therapy on knee joint function and synovial fluid cytokine levels in patients with knee osteoarthritis. Mol Med Rep. 2013 Jan;7(1):183-6. doi: 10.3892/mmr.2012.1168. PMID: 23135204.

Not an outcome of interest – N = 28

1. Anwer S, Alghadir A, Zafar H, et al. Effect of whole body vibration training on quadriceps muscle strength in individuals with knee osteoarthritis: a systematic review and meta-analysis. Physiotherapy. 2015 Oct 22doi: 10.1016/j.physio.2015.10.004. PMID: 26619822.

2. Beckwee D, Bautmans I, Scheerlinck T, et al. Exercise in knee osteoarthritis - preliminary findings: Exercise-induced pain and health status differs between drop-outs and retainers. Exp Gerontol. 2015 Sep 12;72:29-37. doi: 10.1016/j.exger.2015.09.009. PMID: 26368538.

3. Bove A, Smith K, Bise C, et al. What Is the Most Cost-Effective Physical Therapy Strategy to Treat Knee Osteoarthritis? [abstract]. 2015 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2015;67 (suppl 10):1001.

4. Burrows NJ, Booth J, Sturnieks DL, et al. Acute resistance exercise and pressure pain sensitivity in knee osteoarthritis: a randomised crossover trial. Osteoarthritis Cartilage. 2014 Mar;22(3):407-14. doi: 10.1016/j.joca.2013.12.023. PMID: 24418672.

5. Christensen P, Bliddal H, Bartels E, et al. Long-term intervention with weight loss in patients with concomitant obesity and knee osteoarthritis: A randomized trial (the LIGHT study) (ClinicalTrials.gov Identifier: NCT00938808). Obesity reviews; 2014. p. 152.

6. Elboim-Gabyzon M, Rozen N, Laufer Y. The effect of electrical stimulation to the quadriceps muscle combined with group exercise on pain and function in knee osteoarthritis. Physiotherapy (United Kingdom); 2011. p. S3s08.

7. Englund M, Zhang F, Guermazi A, et al. The Effect of Arthroscopic Partial Meniscectomy in Patients with Osteoarthritis on Meniscal Body Extrusion [abstract]. Arthritis Rheumatol. 2015;67 (suppl 10).

8. Gamache T, Price LL, Driban JB, et al. Education Effects on Outcome Expectations for Exercise in Adults with Knee Osteoarthritis [abstract]. 2014 ACR/ARHP Annual Meeting. Arthritis rheumatol. 2014;66 (suppl S10):S1249.

9. Henriksen M, Christensen R, Hunter DJ, et al. Structural changes in the knee during weight loss maintenance after a significant weight loss in obese patients with osteoarthritis: a report of secondary outcome analyses from a randomized controlled trial. Osteoarthritis Cartilage. 2014 May;22(5):639-46. doi: 10.1016/j.joca.2014.03.003. PMID: 24636948.

10. Huang S, Sayre EC, Cibere J. Factors Associated with Physical Therapy Use in Osteoarthritis of the Knee: Results from a Population-Based Study. Arthritis Rheumatol. . 2015;67(suppl 10).

11. Hunter DJ, Beavers DP, Eckstein F, et al. The Intensive Diet and Exercise for Arthritis (IDEA) trial: 18-month radiographic and MRI outcomes. Osteoarthritis Cartilage. 2015 Jul;23(7):1090-8. doi: 10.1016/j.joca.2015.03.034. PMID: 25887362.

12. Kim YS, Choi YJ, Suh DS, et al. Mesenchymal stem cell implantation in osteoarthritic knees: is fibrin glue effective as a scaffold? Am J Sports Med. 2015 Jan;43(1):176-85. doi: 10.1177/0363546514554190. PMID: 25349263.

13. Klokker L, Bandak E, Bartholdy C, et al. Pain in activity evaluation (PACE) in knee osteoarthritis-responsiveness and concurrent validity of tentative measures in a randomized controlled exercise study. Osteoarthritis and cartilage; 2014. p. S187.

14. Knoop J, Steultjens MP, Roorda LD, et al. Improvement in upper leg muscle strength underlies beneficial effects of exercise therapy in knee osteoarthritis: secondary analysis from a randomised controlled trial. Physiotherapy. 2015 Jun;101(2):171-7. doi: 10.1016/j.physio.2014.06.002. PMID: 25280604.

15. Knoop J, van der Leeden M, Roorda LD, et al. Knee joint stabilization therapy in patients with osteoarthritis of the knee and knee instability: subgroup analyses in a randomized, controlled trial. J Rehabil Med. 2014 Jul;46(7):703-7. doi: 10.2340/16501977-1809. PMID: 24910399.

16. Koli J, Multanen J, Kujala UM, et al. Effects of Exercise on Patellar Cartilage in Women with Mild Knee Osteoarthritis. Med Sci Sports Exerc. 2015 Sep;47(9):1767-74. doi: 10.1249/mss.0000000000000629. PMID: 25668399.

17. Martel-Pelletier J, Roubille C, Abram F, et al. First-line analysis of the effects of treatment on progression of structural changes in knee osteoarthritis over 24 months: Data from the osteoarthritis initiative progression cohort. Annals of the Rheumatic Diseases. 2015 1;74(3):547-56. PMID: 2015725015 MEDLINE PMID 24336337 (http://www.ncbi.nlm.nih.gov/pubmed/24336337) FULL TEXT LINK http://dx.doi.org/10.1136/annrheumdis-2013-203906.

18. Meng CP, Katherine N, Leona Y, et al. Outcome Study of Non-operative Treatment for Knee Osteoarthritis in Middle-aged Patients With Reference to the Body Mass Index-A Randomised Prospective Study. Journal of Orthopaedics, Trauma and Rehabilitation; 2011. p. 17-20.

19. Monfort J, Escudero P, Orellana C, et al. Condroitin sulfate decreases chemokine levels and synovitis in knee osteoarthritis patients. Arthritis and Rheumatism. 2012 October;64 SUPPL. 10:S473.

20. Onat SS, Unsal Delialioglu S, Ucar D. Exercises in the Treatment of Elderly Patients with Knee Osteoarthritis: Factors Affecting the Efficiency of Patient Education. Turkish Journal of Geriatrics-Turk Geriatri Dergisi. 2013;16(2):166-71. PMID: WOS:000321476400008.

21. Pellegrini C, Song J, Chang RW, et al. Increasing Moderate-to-Vigorous Activity and Decreasing Sedentary Time Are Associated with 2-Year Weight Loss in Obese Persons with or at Risk for Knee Osteoarthritis [abstract]. 2015 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2015;67 (suppl 10):2274.

22. Phillips K, Williams DA, Gammaitoni A, et al. Predicting Response to Osteoarthritis Treatment Based on Patient Reported Outcome Measures and Quantitative Sensory Testing [abstract]. 2015 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2015;67 (suppl 10):1433.

23. Rabago D, Fortney L, Kijowski R, et al. Clinical and magnetic resonance outcomes in a study of prolotherapy for knee osteoarthritis: Evidence for a potential mechanism of action. PM and R; 2013. p. S225.

24. Reid DA, McNair PJ. Effects of a six week lower limb stretching programme on range of motion, peak passive torque and stiffness in people and without osteoarthritis of the knee. New Zealand Journal of Physiotherapy. 2011;39(1) PMID: 104888822.

25. Rezende MU, Farias FES, Silva CAC, et al. Analysis and correlation of physical therapy tests, pain, function and quality of life questionnaires in patients from parqve (project arthritis recovering quality of life by means of education). Osteoporosis international; 2015. p. S239-s40.

26. Sawitzke AD, Shi H, Finco MF, et al. The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: a report from the glucosamine/chondroitin arthritis intervention trial. Arthritis Rheum. 2008 Oct;58(10):3183-91. doi: 10.1002/art.23973. PMID: 18821708.

27. Selvan T, Rajiah K, Nainar MS, et al. A clinical study on glucosamine sulfate versus combination of glucosamine sulfate and NSAIDs in mild to moderate knee osteoarthritis. ScientificWorldJournal. 2012;2012:902676. doi: 10.1100/2012/902676. PMID: 22577354.

28. Villadsen A, Overgaard S, Holsgaard-Larsen A, et al. Immediate efficacy of neuromuscular exercise in patients with severe osteoarthritis of the hip or knee: a secondary analysis from a randomized controlled trial. J Rheumatol. 2014 Jul;41(7):1385-94. doi: 10.3899/jrheum.130642. PMID: 24931956.

Study design – N = 85

1. National Board of Health, Denmark. Referenceprogram for knæartrose. Copenhagen: National Board of Health, Denmark; 2007. Found at: http://www.sst.dk/publ/Publ2007/PLAN/SfR/Refprg_knaeartrose.pdf.

2. Ageberg E, Engstrom G, Gerhardsson de Verdier M, et al. Effect of leisure time physical activity on severe knee or hip osteoarthritis leading to total joint replacement: a population-based prospective cohort study. BMC Musculoskelet Disord. 2012;13:73. doi: 10.1186/1471-2474-13-73. PMID: 22595023.

3. Al-Johani AH, Kachanathu SJ, Ramadan Hafez A, et al. Comparative study of hamstring and quadriceps strengthening treatments in the management of knee osteoarthritis. J Phys Ther Sci. 2014 Jun;26(6):817-20. doi: 10.1589/jpts.26.817. PMID: 25013274.

4. Andia I, Maffulli N. Platelet-rich plasma for managing pain and inflammation in osteoarthritis. Nature Reviews Rheumatology. 2013 Dec;9(12):721-30. PMID: WOS:000328126000005.

5. Bar-Ziv Y, Debbi EM, Ran Y, et al. Long-Term Effects of AposTherapy in Patients with Osteoarthritis of the Knee: A Two-Year Followup. Arthritis. 2013;2013:689236. doi: 10.1155/2013/689236. PMID: 23533753.

6. Beumer L, Wong JN, Warden SJ, et al. Effects of exercise and manual therapy on pain associated with hip osteoarthritis: a systematic review and meta-analysis. British Journal of Sports Medicine. 2016 Apr;50(8):458-U29. doi: 10.1136/bjsports-2015-095255. PMID: WOS:000373706000006.

7. Bressel E, Wing JE, Miller AI, et al. High-intensity interval training on an aquatic treadmill in adults with osteoarthritis: effect on pain, balance, function, and mobility. J Strength Cond Res. 2014 Aug;28(8):2088-96. doi: 10.1519/jsc.0000000000000258. PMID: 25057845.

8. Brosseau L, et al. Efficacy of transcutaneous electrical nerve stimulation for osteoarthritis of the lower extremities: a meta-analysis. Physical Therapy Reviews. 2004;9(4):213-33.

9. Brouwer RW, van Raaij TM, Jakma TT, et al. Braces and orthoses for treating osteoarthritis of the knee. Cochrane Database of Systematic Reviews. 2015(3):N.PAG-N.PAG. doi: 10.1002/14651858.CD004020.pub3. PMID: 105838166. Language: English. Entry Date: 20101029. Revision Date: 20151007. Publication Type: Journal Article.

10. Brumini C, Natour J, Miura L, et al. Effectiveness of bracing in elderly with knee osteoartritis: A randomized controlled trial. Annals of the rheumatic diseases; 2015. p. 1311.

11. Bruyere O, Cooper C, Pelletier JP, et al. A consensus statement on the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for the management of knee osteoarthritis-From evidence-based medicine to the real-life setting. Semin Arthritis Rheum. 2016 Feb;45(4 Suppl):S3-11. doi: 10.1016/j.semarthrit.2015.11.010. PMID: 26806188.

12. Carmona-Teres V, Lumillo-Gutierrez I, Jodar-Fernandez L, et al. Effectiveness and cost-effectiveness of a health coaching intervention to improve the lifestyle of patients with knee osteoarthritis: cluster randomized clinical trial. BMC Musculoskelet Disord. 2015;16:38. doi: 10.1186/s12891-015-0501-x. PMID: 25887078.

13. Chang WD, Chen S, Lee CL, et al. The Effects of Tai Chi Chuan on Improving Mind-Body Health for Knee Osteoarthritis Patients: A Systematic Review and Meta-Analysis. Evid Based Complement Alternat Med. 2016;2016:1813979. doi: 10.1155/2016/1813979. PMID: 27635148.

14. Cherian JJ, Harrison PE, Benjamin SA, et al. Do the Effects of Transcutaneous Electrical Nerve Stimulation on Knee Osteoarthritis Pain and Function Last? J Knee Surg. 2015 Nov 5doi: 10.1055/s-0035-1566735. PMID: 26540652.

15. Cheung CK, Wyman J, Bronas U, et al. Is yoga better than aerobic/strengthening exercises for managing knee osteoarthritis in older adults? Osteoarthritis and Cartilage. 2016 April;24 SUPPL. 1:S484.

16. Coudeyre E, Jegu AG, Giustanini M, et al. Isokinetic muscle strengthening for knee osteoarthritis: A systematic review of randomized controlled trials with meta-analysis. Ann Phys Rehabil Med. 2016 Jun;59(3):207-15. doi: 10.1016/j.rehab.2016.01.013. PMID: 27079585.

17. Dai Z, Liu HS, Wang SJ, et al. [Efficacy evaluation on knee osteoarthritis treated with acupuncture: non-randomized concurrent control trial]. Zhongguo Zhen Jiu. 2014 Apr;34(4):329-33. PMID: 24946628.

18. Emadedin M, Ghorbani Liastani M, Fazeli R, et al. Long-Term Follow-up of Intra-articular Injection of Autologous Mesenchymal Stem Cells in Patients with Knee, Ankle, or Hip Osteoarthritis. Arch Iran Med. 2015 Jun;18(6):336-44. doi: 015186/aim.003. PMID: 26058927.

19. Filardo G, Kon E, Pereira Ruiz MT, et al. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: single- versus double-spinning approach. Knee Surg Sports Traumatol Arthrosc. 2012 Oct;20(10):2082-91. doi: 10.1007/s00167-011-1837-x. PMID: 22203046.

20. Finger S, Paulos LE. Clinical and biomechanical evaluation of the unloading brace. J Knee Surg. 2002 Summer;15(3):155-8; discussion 9. PMID: 12152976.

21. Fitzgerald GK, Hinman RS, Zeni J, Jr., et al. OARSI Clinical Trials Recommendations: Design and conduct of clinical trials of rehabilitation interventions for osteoarthritis. Osteoarthritis Cartilage. 2015 May;23(5):803-14. doi: 10.1016/j.joca.2015.03.013. PMID: 25952351.

22. Forestier R, Erol Forestier FB, Francon A. Spa therapy and knee osteoarthritis: A systematic review. Ann Phys Rehabil Med. 2016 Jun;59(3):216-26. doi: 10.1016/j.rehab.2016.01.010. PMID: 26996955.

23. Foster N, Nicholls E, Holden M, et al. Improving the effectiveness of exercise therapy for older adults with knee osteoarthritis: A pragmatic randomised controlled trial (the beep trial). Annals of the rheumatic diseases; 2015. p. 108.

24. Fransen M, McConnell S. Exercise for osteoarthritis of the knee. Cochrane Database of Systematic Reviews. 2015(1):N.PAG-N.PAG. PMID: 105837896. Language: English. Entry Date: 20111014. Revision Date: 20150711. Publication Type: Journal Article.

25. Ghasemi GA, Golkar A, Marandi SM. Effects of hata yoga on knee osteoarthritis. Int J Prev Med. 2013 Apr;4(Suppl 1):S133-8. PMID: 23717763.

26. Golightly YM, Allen KD, Caine DJ. A comprehensive review of the effectiveness of different exercise programs for patients with osteoarthritis. Phys Sportsmed. 2012 Nov;40(4):52-65. doi: 10.3810/psm.2012.11.1988. PMID: 23306415.

27. Gomes WF, Lacerda AC, Mendonca VA, et al. Effect of exercise on the plasma BDNF levels in elderly women with knee osteoarthritis. Rheumatol Int. 2014 Jun;34(6):841-6. doi: 10.1007/s00296-013-2786-0. PMID: 23739920.

28. Grotle M. Traditional Chinese acupuncture was not superior to sham acupuncture for knee osteoarthritis but delivering treatment with high expectations of improvement was superior to delivering treatment with neutral expectations. J Physiother. 2011;57(1):56. doi: 10.1016/s1836-9553(11)70009-1. PMID: 21402332.

29. Habib G, Zahran R, Najjar R, et al. The effect of intra-articular injection of Diprospan at the knee joint on the hypothalamic-pituitary-adrenal axis. Swiss Medical Weekly. 2015 May;145 PMID: WOS:000355008600001.

30. Hayta E, Senel O, Hizmetli S, et al. Investigation of short-wave diathermy genotoxic effect in patients with knee osteoarthritis. Clinical and experimental rheumatology; 2014. p. S71-s2.

31. Henriksen M, Hansen J, Klokker L, et al. Exercise versus analgesics for knee osteoarthritis pain: A meta-epidemiological study of cochrane systematic reviews. Osteoarthritis and cartilage; 2015. p. A172.

32. Henriksen M, Hansen JB, Klokker L, et al. Comparable effects of exercise and analgesics for pain secondary to knee osteoarthritis: a meta-analysis of trials included in Cochrane systematic reviews. J Comp Eff Res. 2016 Jul;5(4):417-31. doi: 10.2217/cer-2016-0007. PMID: 27346368.

33. Hurley M, Walsh NE, Oliver S, et al. The Physical and Psychosocial Effects of Exercise on Chronic Hip and Knee Pain: A Cochrane Review with Meta-Analysis [abstract]. 2014 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2014;66 (suppl S10):S1016.

34. Ip D. Does addition of low-level laser therapy (LLLT) in conservative care of knee arthritis successfully postpone the need for joint replacement? Lasers Med Sci. 2015 Sep 29doi: 10.1007/s10103-015-1814-6. PMID: 26420240.

35. Jaiswal PK, Bentley G, Carrington RWJ, et al. The adverse effect of elevated body mass index on outcome after autologous chondrocyte implantation. Journal of Bone and Joint Surgery-British Volume. 2012 Oct;94B(10):1377-81. PMID: WOS:000309355400014.

36. Jang SJ. The application of platelet-rich plasma in early osteoarthritis of knee. Osteoarthritis and Cartilage. 2011 September;19 SUPPL. 1:S145.

37. Jones RK, Nester CJ, Richards JD, et al. A comparison of the biomechanical effects of valgus knee braces and lateral wedged insoles in patients with knee osteoarthritis. Gait Posture. 2013 Mar;37(3):368-72. doi: 10.1016/j.gaitpost.2012.08.002. PMID: 22920242.

38. Jordan KM, Arden NK, Doherty M, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2003 Dec;62(12):1145-55. PMID: 14644851.

39. Kanchanatawan W, Arirachakaran A, Chaijenkij K, et al. Short-term outcomes of platelet-rich plasma injection for treatment of osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc. 2016 May;24(5):1665-77. doi: 10.1007/s00167-015-3784-4. PMID: 26387122.

40. Kao MJ, Wu MP, Tsai MW, et al. The effectiveness of a self-management program on quality of life for knee osteoarthritis (OA) patients. Arch Gerontol Geriatr. 2012 Mar-Apr;54(2):317-24. doi: 10.1016/j.archger.2011.05.018. PMID: 21726907.

41. Kim EJ, Lim CY, Lee EY, et al. Comparing the effects of individualized, standard, sham and no acupuncture in the treatment of knee osteoarthritis: a multicenter randomized controlled trial. Trials. 2013;14:129. doi: 10.1186/1745-6215-14-129. PMID: 23782709.

42. Kim TH, Kim KH, Kang JW, et al. Moxibustion treatment for knee osteoarthritis: a multi-centre, non-blinded, randomised controlled trial on the effectiveness and safety of the moxibustion treatment versus usual care in knee osteoarthritis patients. PLoS One. 2014;9(7):e101973. doi: 10.1371/journal.pone.0101973. PMID: 25061882.

43. Kim TH, Kim KH, Kang JW, et al. Moxibustion treatment for knee osteoarthritis: A multi-centre, non-blinded, randomised controlled trial. Integrative Medicine Research; 2015. p. 13.

44. Kim YS, Choi YJ, Koh YG. Mesenchymal stem cell implantation in knee osteoarthritis: an assessment of the factors influencing clinical outcomes. Am J Sports Med. 2015 Sep;43(9):2293-301. doi: 10.1177/0363546515588317. PMID: 26113522.

45. Komistek RD, Dennis DA, Northcut EJ, et al. An in vivo analysis of the effectiveness of the osteoarthritic knee brace during heel-strike of gait. J Arthroplasty. 1999 Sep;14(6):738-42. PMID: 10512447.

46. Korkmaz M, Karaaslan F, Erdogan Y, et al. Efficacy of treatment with glucosamine sulfate in patients with knee effusion due to osteoarthritis. Pak J Med Sci. 2013 May;29(3):847-50. PMID: 24353641.

47. Lau MC, Lam JK, Siu E, et al. Physiotherapist-designed aquatic exercise programme for community-dwelling elders with osteoarthritis of the knee: a Hong Kong pilot study. Hong Kong Med J. 2014 Feb;20(1):16-23. doi: 10.12809/hkmj133931. PMID: 24021934.

48. Lee HY, Lee KJ. [Effects of Tai Chi exercise in elderly with knee osteoarthritis]. Taehan Kanho Hakhoe chi; 2008. p. 11-8.

49. Li X, Wang XQ, Chen BL, et al. Whole-Body Vibration Exercise for Knee Osteoarthritis: A Systematic Review and Meta-Analysis (vol 2015, 758147, 2015). Evidence-Based Complementary and Alternative Medicine. 2015doi: 10.1155/2015/636435. PMID: WOS:000365904900001.

50. Lindenfeld TN, Hewett TE, Andriacchi TP. Joint loading with valgus bracing in patients with varus gonarthrosis. Clin Orthop Relat Res. 1997 Nov(344):290-7. PMID: 9372780.

51. Lu M, Su Y, Zhang Y, et al. Effectiveness of aquatic exercise for treatment of knee osteoarthritis: Systematic review and meta-analysis ORIGINAL (NON-ENGLISH) TITLE Wirksamkeit von Wassergymnastik bei Kniegelenksarthrose: Systematische Übersicht und Metaanalyse. Zeitschrift fur Rheumatologie. 2015 19;74(6):543-52. PMID: 2015759057 FULL TEXT LINK http://dx.doi.org/10.1007/s00393-014-1559-9.

52. Maa SH, Sun MF, Wu CC. The effectiveness of acupuncture on pain and mobility in patients with osteoarthritis of the knee: a pilot study. J Nurs Res. 2008 Jun;16(2):140-8. PMID: 18528820.

53. Marcu RI, Traistaru R, Patru S, et al. Rehabilitation program improves functional status and quality of life in patients with knee osteoarthritis. Annals of the Rheumatic Diseases. 2015 June;74 SUPPL. 2:1192.

54. McAlindon TE, Driban JB, Henrotin Y, et al. OARSI Clinical Trials Recommendations: Design, conduct, and reporting of clinical trials for knee osteoarthritis. Osteoarthritis Cartilage. 2015 May;23(5):747-60. doi: 10.1016/j.joca.2015.03.005. PMID: 25952346.

55. Meheux CJ, McCulloch PC, Lintner DM, et al. Efficacy of Intra-articular Platelet-Rich Plasma Injections in Knee Osteoarthritis: A Systematic Review. Arthroscopy - Journal of Arthroscopic and Related Surgery. 2016 1;32(3):495-505. PMID: 2015555642 FULL TEXT LINK http://dx.doi.org/10.1016/j.arthro.2015.08.005.

56. Micca JL, Ruff D, Ahl J, et al. Safety and efficacy of duloxetine treatment in older and younger patients with osteoarthritis knee pain: a post hoc, subgroup analysis of two randomized, placebo-controlled trials. BMC Musculoskelet Disord. 2013;14:137. doi: 10.1186/1471-2474-14-137. PMID: 23590727.

57. Mine K, Nakayama T, Milanese S, et al. The effectiveness of braces and orthoses for patients with knee osteoarthritis: A systematic review of Japanese-language randomised controlled trials. Prosthet Orthot Int. 2016 Apr 26doi: 10.1177/0309364616640926. PMID: 27117012.

58. Moe RH, Fernandes L, Osteras N. Daily use of a cane for two months reduced pain and improved function in patients with knee osteoarthritis. J Physiother. 2012;58(2):128. doi: 10.1016/s1836-9553(12)70094-2. PMID: 22613244.

59. Nadaud MC, Komistek RD, Mahfouz MR, et al. In vivo three-dimensional determination of the effectiveness of the osteoarthritic knee brace: a multiple brace analysis. J Bone Joint Surg Am. 2005;87 Suppl 2:114-9. doi: 10.2106/JBJS.E.00482. PMID: 16326730.

60. Nambi GS, Shah AA. Additional effect of iyengar yoga and EMG biofeedback on pain and functional disability in chronic unilateral knee osteoarthritis. Int J Yoga. 2013 Jul;6(2):123-7. doi: 10.4103/0973-6131.113413. PMID: 23930031.

61. Oiestad BE. Multi-modal realignment treatment decreases pain in people with medial tibiofemoral osteoarthritis. J Physiother. 2012;58(4):272. doi: 10.1016/s1836-9553(12)70132-7. PMID: 23177233.

62. Osiri M, al. e. Transcutaneous electrical nerve stimulation for knee osteoarthritis (Review). 2009.

63. Pagani CH, Bohle C, Potthast W, et al. Short-term effects of a dedicated knee orthosis on knee adduction moment, pain, and function in patients with osteoarthritis. Arch Phys Med Rehabil. 2010 Dec;91(12):1936-41. doi: 10.1016/j.apmr.2010.09.003. PMID: 21112437.

64. Park J, McCaffrey R, Newman D, et al. The Effect of Sit 'N' Fit Chair Yoga Among Community-Dwelling Older Adults With Osteoarthritis. Holistic Nursing Practice. 2014 Jul-Aug;28(4):247-57. PMID: WOS:000338446200006.

65. Peeler J, Christian M, Cooper J, et al. Managing Knee Osteoarthritis: The Effects of Body Weight Supported Physical Activity on Joint Pain, Function, and Thigh Muscle Strength. Clin J Sport Med. 2015 Nov;25(6):518-23. doi: 10.1097/jsm.0000000000000173. PMID: 25647537.

66. Piyakhachornrot N, Aree-Ue S, Putwatana P, et al. Impact of an integrated health education and exercise program in middle-aged Thai adults with osteoarthritis of the knee. Orthop Nurs. 2011 Mar-Apr;30(2):134-42. doi: 10.1097/NOR.0b013e31821130bf. PMID: 21422897.

67. Pollo FE. Bracing and heel wedging for unicompartmental osteoarthritis of the knee. The American journal of knee surgery. 1997;11(1):47-50.

68. Rabago D, Mundt M, Zgierska A, et al. Hypertonic dextrose injection (prolotherapy) for knee osteoarthritis: Long term outcomes. Complement Ther Med. 2015 Jun;23(3):388-95. doi: 10.1016/j.ctim.2015.04.003. PMID: 26051574.

69. Regnaux JP, Lefèvre-Colau MM, Trinquart L, et al. High-Intensity Versus Low-Intensity Physical Activity or Exercises in Patients with Hip or Knee Osteoarthritis: A Meta-Analysis [abstract]. 2015 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2015;67 (suppl 10):2414.

70. Rooij M, Leeden M, Cheung J, et al. Effectiveness of tailored exercise therapy in patients with knee osteoarthritis and comorbidity: A randomized controlled trial. Osteoarthritis and cartilage; 2016. p. S466-s7.

71. Rosa UH, Velasquez Tlapanco J, Lara Maya C, et al. Comparison of the effectiveness of isokinetic vs isometric therapeutic exercise in patients with osteoarthritis of knee. [Spanish]. Reumatologia clinica; 2012. p. 10-4.

72. Rutgers M, Creemers LB, Yang KGA, et al. Osteoarthritis treatment using autologous conditioned serum after placebo Patient considerations and clinical response in a non-randomized case series. Acta Orthopaedica. 2015 Feb;86(1):114-8. PMID: WOS:000348367000018.

73. Ryo T, Junya O, Nobuhiro K, et al. Does exercise therapy improve the health-related quality of life of people with knee osteoarthritis? A systematic review and meta-analysis of randomized controlled trials. Journal of Physical Therapy Science. 2015;27(10):3309-14. PMID: 110815137. Language: English. Entry Date: 20160212. Revision Date: 20160212. Publication Type: Article. Journal Subset: Allied Health.

74. Sanchez M, Anitua E, Azofra J, et al. Intra-articular injection of an autologous preparation rich in growth factors for the treatment of knee OA: a retrospective cohort study. Clin Exp Rheumatol. 2008 Sep-Oct;26(5):910-3. PMID: 19032827.

75. Self BP, Greenwald RM, Pflaster DS. A biomechanical analysis of a medial unloading brace for osteoarthritis in the knee. Arthritis Care Res. 2000 Aug;13(4):191-7. PMID: 14635273.

76. Shainhouse J, Patrick J, Argoff C. Open-label, open-ended study of the safety of diclofenac topical solution for management of osteoarthritis: Characterization of application-site adverse events. Osteoarthritis and Cartilage. 2011 September;19 SUPPL. 1:S231.

77. Shereif WI, Hassanin AA. Comparison between Uses of Therapeutic Exercise and Heat Application on Relieve Pain, Stiffness and Improvement of Physical Function for Patient with Knee Osteoarthritis. Life Science Journal-Acta Zhengzhou University Overseas Edition. 2011;8(3):388-96. PMID: WOS:000303523200061.

78. Srivastava R, Avasthi V, Srivastava S, et al. Does yoga improve pain, stiffness and physical disability in knee osteoarthritis?-A randomize controlled clinical trial. Osteoarthritis and cartilage; 2015. p. A167.

79. Tanaka R, Ozawa J, Kito N, et al. Does exercise therapy improve health-related quality of life in people with knee osteoarthritis? a systematic review. Annals of the Rheumatic Diseases. 2015 June;74 SUPPL. 2:157-8.

80. Trombini-Souza F, Fuller R, Matias A, et al. Effectiveness of a long-term use of a minimalist footwear versus habitual shoe on pain, function and mechanical loads in knee osteoarthritis: A randomized controlled trial. BMC Musculoskeletal Disorders. 2012;13(121) PMID: 2012543191 MEDLINE PMID 22788574 (http://www.ncbi.nlm.nih.gov/pubmed/22788574) FULL TEXT LINK http://dx.doi.org/10.1186/1471-2474-13-121.

81. Wallis JA, Webster KE, Levinger P, et al. A pre-operative group rehabilitation programme provided limited benefit for people with severe hip and knee osteoarthritis. Disabil Rehabil. 2014;36(24):2085-90. doi: 10.3109/09638288.2014.895428. PMID: 24597936.

82. Watanabe S, Someya F. Effect of Body Weight-supported Walking on Exercise Capacity and Walking Speed in Patients with Knee Osteoarthritis: A Randomized Controlled Trial. J Jpn Phys Ther Assoc. 2013;16(1):28-35. doi: 10.1298/jjpta.Vol16_004. PMID: 25792901.

83. Yang SB, Eaton CB, McAlindon TE, et al. Effects of Glucosamine and Chondroitin Supplementation on Knee Osteoarthritis. Arthritis & Rheumatology. 2015 Mar;67(3):714-23. PMID: WOS:000350300400016.

84. Yu D, Xie HW, Zhang B, et al. [Observation on clinical effects of moxibustion stimulation of different sensitive status acupoints for knee osteoarthritis]. Zhen Ci Yan Jiu. 2013 Dec;38(6):497-501. PMID: 24579366.

85. Zohra HF, Souad M, Mustapha R, et al. Exercise therapy for osteoarthritis of the knee: Two years follow up. Clinical and Experimental Rheumatology. 2014 2014;32(4 SUPPL. 83):S84.

Study was included in a previous SR – N = 3

1. Baker K, Goggins J, Xie H, et al. A randomized crossover trial of a wedged insole for treatment of knee osteoarthritis. Arthritis and rheumatism; 2007. p. 1198-203.

2. Bennell KL, Bowles KA, Payne C, et al. Effects of lateral wedge insoles on symptoms and structural disease progression in medial knee osteoarthritis: a 12-month randomised controlled trial. Osteoarthritis and cartilage; 2010. p. S11.

3. Kirkley A, Webster-Bogaert S, Litchfield R, et al. The effect of bracing on varus gonarthrosis. J Bone Joint Surg Am. 1999 Apr;81(4):539-48. PMID: 10225800.

Maximum followup is less than 30 days – N = 36

1. Ahsin S, Saleem S, Bhatti AM, et al. Clinical and endocrinological changes after electro-acupuncture treatment in patients with osteoarthritis of the knee. Pain. 2009 Dec 15;147(1-3):60-6. doi: 10.1016/j.pain.2009.08.004. PMID: 19766392.

2. Altay F, Durmus D, Canturk F. Effects of TENS on pain, disabiliy, quality of life and depression in patients with knee osteoarthritis. [Turkish]. Turkish Journal of Rheumatology; 2010. p. 116-21.

3. Anandkumar S, Sudarshan S, Nagpal P. Efficacy of kinesio taping on isokinetic quadriceps torque in knee osteoarthritis: a double blinded randomized controlled study. Physiother Theory Pract. 2014 Aug;30(6):375-83. doi: 10.3109/09593985.2014.896963. PMID: 24617598.

4. Basic-Kapidzic N, Imsirovic A, Music A. Measurement of therapeutic effect of ultrasound on knee osteoarthritis; double blind study. Annals of the Rheumatic Disease; 2013.

5. Basu S, Palekar TJ, Balasaravanan R. Comparative study of analgesic along with taping technique versus analgesic along with cryotherapy in unilateral patello-femoral osteoarthritis of knee joint. International Journal of Pharma and Bio Sciences. 2014 April/June;5(2):B361-B73. PMID: 2014255229.

6. Boyaci A, Tutoglu A, Boyaci N, et al. Comparison of the efficacy of ketoprofen phonophoresis, ultrasound, and short-wave diathermy in knee osteoarthritis. Rheumatol Int. 2013 Nov;33(11):2811-8. doi: 10.1007/s00296-013-2815-z. PMID: 23832291.

7. Cheng G, Cheng W, Jiang YG. [Controlled observation of clinical efficacy on knee osteoarthritis treated with auricular electroacupuncture and the isolated moxibustion with Lingxian herbal paste]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion; 2014. p. 230-4.

8. Chiranthanut N, Hanprasertpong N. Thai massage, and Thai herbal compress versus oral ibuprofen in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. 2014;2014:490512. doi: 10.1155/2014/490512. PMID: 25254207.

9. Cho HY, Kim EH, Kim J, et al. Kinesio taping improves pain, range of motion, and proprioception in older patients with knee osteoarthritis: a randomized controlled trial. Am J Phys Med Rehabil. 2015 Mar;94(3):192-200. doi: 10.1097/phm.0000000000000148. PMID: 25706053.

10. Daskapan A, Anaforoglu B, Ozunlu Pekyavas N, et al. Comparison of mini-squats and straight leg raises in patients with knee osteoarthritis: A randomized controlled clinical trial. Turkish Journal of Rheumatology; 2013. p. 16-26.

11. Espejo Antunez L, Caro Puertolas B, Ibanez Burgos B, et al. Effects of mud therapy on perceived pain and quality of life related to health in patients with knee osteoarthritis. Reumatol Clin. 2013 May-Jun;9(3):156-60. doi: 10.1016/j.reuma.2012.09.005. PMID: 23357640.

12. Fioravanti A, Giannitti C, Cheleschi S, et al. Circulating levels of adiponectin, resistin, and visfatin after mud-bath therapy in patients with bilateral knee osteoarthritis. Int J Biometeorol. 2015 Nov;59(11):1691-700. doi: 10.1007/s00484-015-0977-y. PMID: 25750093.

13. Geler Kulcu D, Yanik B, Gulsen G, et al. Effect of neuromuscular electrical stimulation on pain and functional parameters in knee osteoarthritis. [Turkish]. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi; 2009. p. 111-5.

14. Gundog M, Atamaz F, Kanyilmaz S, et al. Interferential current therapy in patients with knee osteoarthritis: comparison of the effectiveness of different amplitude-modulated frequencies. Am J Phys Med Rehabil. 2012 Feb;91(2):107-13. doi: 10.1097/PHM.0b013e3182328687. PMID: 22019968.

15. Habib G, Safia A. The effect of intra-articular injection of betamethasone acetate/betamethasone sodium phosphate on blood glucose levels in controlled diabetic patients with symptomatic osteoarthritis of the knee. Clin Rheumatol. 2009 Jan;28(1):85-7. doi: 10.1007/s10067-008-1023-9. PMID: 18853221.

16. Hanafy AF, Megeid Abdallah AAA. Quadriceps strength, knee pain and functional performance with patellar taping in knee osteoarthritis. Journal of musculoskeletal research; 2014.

17. Hu QS, Zhang QR, Jia CS, et al. [Randomized controlled clinical trials of red-hot filiform needle puncturing for knee ostarthritis and inflammatory cytokines in knee articular fluid in senile knee ostarthritis patients]. Zhen Ci Yan Jiu. 2011 Apr;36(2):110-5. PMID: 21717778.

18. Karner M, Brazkiewicz F, Remppis A, et al. Objectifying specific and nonspecific effects of acupuncture: a double-blinded randomised trial in osteoarthritis of the knee. Evid Based Complement Alternat Med. 2013;2013:427265. doi: 10.1155/2013/427265. PMID: 23365608.

19. Kim MJ, Lee DH, Kim T, et al. Lower extremity exercise of knee osteoarthritis patients using portable assistive robot (HEXAR-KR40P). International Journal of Precision Engineering and Manufacturing. 2014 Dec;15(12):2617-22. PMID: WOS:000346166800018.

20. Kolen AF, de Nijs RN, Wagemakers FM, et al. Effects of spatially targeted transcutaneous electrical nerve stimulation using an electrode array that measures skin resistance on pain and mobility in patients with osteoarthritis in the knee: a randomized controlled trial. Pain. 2012 Feb;153(2):373-81. doi: 10.1016/j.pain.2011.10.033. PMID: 22119338.

21. Liang YW, Tan YS, Yuan YQ. Observation on the therapeutic effect of modified sparrow-pecking moxibustion for 60 cases of osteoarthritis of knee. World Journal of Acupuncture - Moxibustion; 2013. p. 55-7.

22. Lin MN, Li XH, Liang WN, et al. Needle-knife therapy improves the clinical symptoms of knee osteoarthritis by inhibiting the expression of inflammatory cytokines. Experimental and Therapeutic Medicine. 2014 Apr;7(4):835-42. PMID: WOS:000334299200013.

23. Navali AM, Sadat BE, Hajipour B, et al. Anew Shoe Decreases Pain and Fatigue in Ascending and Descending the stairs in patients with knee osteoarthritis. Life Science Journal-Acta Zhengzhou University Overseas Edition. 2012;9(4):2543-9. PMID: WOS:000316685600008.

24. Pavlovic AS, Djurasic LM. The effect of low frequency pulsing electromagnetic field in treatment of patients with knee joint osteoarthritis. Acta Chir Iugosl. 2012;59(3):81-3. PMID: 23654012.

25. Sahin-Onat S, Tasoglu O, Ozisler Z, et al. Balneotherapy in the treatment of knee osteoarthritis: A controlled study. Archives of Rheumatology; 2015. p. 292-7.

26. Sudhesh P. Effect of taping and closed kinetic chain versus traditional approach in osteoarthritis knee. International Journal of Pharma and Bio Sciences; 2013. p. B1156-b65.

27. Toopchizadeh V, Javadi R, Sadat BE. Therapeutic efficacy of dexamethasone phonophoresis on symptomatic knee osteoarthritis in elderly women. International Journal of Women's Health and Reproduction Sciences. 2014 1;2(3):168-77. PMID: 2014931534 FULL TEXT LINK http://dx.doi.org/10.15296/ijwhr.2014.25.

28. Topp R, Brosky JA, Jr., Pieschel D. The effect of either topical menthol or a placebo on functioning and knee pain among patients with knee OA. J Geriatr Phys Ther. 2013 Apr-Jun;36(2):92-9. doi: 10.1519/JPT.0b013e318268dde1. PMID: 22976810.

29. Tosun A, Beyazova M, Meray J, et al. Efficacy of a Single Dose Transdermal Flurbiprofen Administration in Patients with Knee Osteoarthritis. Turkiye Klinikleri Tip Bilimleri Dergisi. 2010 Dec;30(6):1911-6. PMID: WOS:000287053500018.

30. Ulus Y, Tander B, Akyol Y, et al. Therapeutic ultrasound versus sham ultrasound for the management of patients with knee osteoarthritis: a randomized double-blind controlled clinical study. Int J Rheum Dis. 2012 Apr;15(2):197-206. doi: 10.1111/j.1756-185X.2012.01709.x. PMID: 22462424.

31. van den Noort J, van der Esch M, Steultjens MP, et al. Influence of the instrumented force shoe on gait pattern in patients with osteoarthritis of the knee. Medical & Biological Engineering & Computing. 2011 Dec;49(12):1381-92. PMID: WOS:000297550600005.

32. Vance CG, Rakel BA, Blodgett NP, et al. Effects of transcutaneous electrical nerve stimulation on pain, pain sensitivity, and function in people with knee osteoarthritis: a randomized controlled trial. Phys Ther. 2012 Jul;92(7):898-910. doi: 10.2522/ptj.20110183. PMID: 22466027.

33. Varadi G, Zhu Z, Blattler T, et al. Randomized clinical trial evaluating transdermal Ibuprofen for moderate to severe knee osteoarthritis. Pain Physician. 2013 Nov-Dec;16(6):E749-62. PMID: 24284856.

34. Varadi G, Zhu Z, Blättler T, et al. Randomized clinical trial evaluating transdermal ibuprofen for moderate to severe knee osteoarthritis. Pain Physician. 2013;16(6):E749-E62.

35. Wang YB, Huang XY, Song B, et al. Comparative study of drug intervention in treatment of rural middle-aged and elderly people with knee osteoarthritis in Fengxian District, Shanghai. African Journal of Pharmacy and Pharmacology. 2012 Jun;6(24):1741-5. PMID: WOS:000307967000005.

36. Zhang QR, Fu WB. [Osteoarthritis of knee joint treated with acupuncture and moxibustion]. Zhongguo Zhen Jiu. 2010 May;30(5):375-8. PMID: 20518172.

Comparators not of interest – N = 70

1. Ali SS, Ahmed SI, Khan M, et al. Comparing the effects of manual therapy versus electrophysical agents in the management of knee osteoarthritis. Pak J Pharm Sci. 2014 Jul;27(4 Suppl):1103-6. PMID: 25016274.

2. Allen KD, Bongiorni D, Bosworth HB, et al. Group Versus Individual Physical Therapy for Veterans With Knee Osteoarthritis: Results of a Randomized Clinical Trial. Phys Ther. 2015 Nov 19doi: 10.2522/ptj.20150194. PMID: 26586865.

3. Angoorani H, Mazaherinezhad A, Marjomaki O, et al. Treatment of knee osteoarthritis with platelet-rich plasma in comparison with transcutaneous electrical nerve stimulation plus exercise: a randomized clinical trial. Med J Islam Repub Iran. 2015;29:223. PMID: 26478881.

4. Ashraf A, Zarei F, Hadianfard MJ, et al. Comparison the effect of lateral wedge insole and acupuncture in medial compartment knee osteoarthritis: A randomized controlled trial. Knee. 2014 March;21(2):439-44. PMID: 2014231288 MEDLINE PMID 24462108 (http://www.ncbi.nlm.nih.gov/pubmed/24462108) FULL TEXT LINK http://dx.doi.org/10.1016/j.knee.2013.12.002.

5. Brandao GDC, Korukian M, Brandao DDC, et al. Association of glucosamine sulphate and chondroitin sulphate for patients with osteoarthritis of the knee ORIGINAL (NON-ENGLISH) TITLE Associacao de sulfato de glicosamina e sulfato de condroitina para pacientes portadores de osteoartrose de joelho. Revista Brasileira de Medicina. 2009 November;66(11):405-8. PMID: 2010034475.

6. Bui B, Nguyen L. Efficacy of PRP injection in treatment of primary knee OA. International Journal of Rheumatic Diseases. 2014 April;17 SUPPL. 1:35.

7. Byeon GJ, Kim KH. Piriformis syndrome in knee osteoarthritis patients after wearing rocker bottom shoes. Korean J Pain. 2011 Jun;24(2):93-9. doi: 10.3344/kjp.2011.24.2.93. PMID: 21716617.

8. Cerza F, Carni S, Carcangiu A, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. Am J Sports Med. 2012 Dec;40(12):2822-7. doi: 10.1177/0363546512461902. PMID: 23104611.

9. Chen R, Chen M, Su T, et al. Heat-sensitive moxibustion in patients with osteoarthritis of the knee: a three-armed multicentre randomised active control trial. Acupunct Med. 2015 May 21doi: 10.1136/acupmed-2014-010740. PMID: 25998755.

10. Chen WL, Hsu WC, Lin YJ, et al. Comparison of intra-articular hyaluronic acid injections with transcutaneous electric nerve stimulation for the management of knee osteoarthritis: a randomized controlled trial. Arch Phys Med Rehabil. 2013 Aug;94(8):1482-9. doi: 10.1016/j.apmr.2013.04.009. PMID: 23628378.

11. Cheng Y, Wu K, Cheng Z, et al. [Randomized controlled study on the treatment of knee osteoarthritis with different acupuncture methods at different stages]. [Chinese]. Zhongguo zhen jiu [Chinese acupuncture & moxibustion]; 2013. p. 508-12.

12. Cutovic M, Jovic S, Konstantinovic L, et al. [The effects of balneotherapy on knee osteoarthritis]. Med Pregl. 2006;59 Suppl 1:47-50. PMID: 17361596.

13. Deng CL, Li J, Cao XW, et al. Therapeutic Effectiveness Evaluation on Shishi Manipulation for Knee Osteoarthritis. 2012 Ieee International Conference on Bioinformatics and Biomedicine Workshops. 2012.

14. Deng N, Ran QF, Jin T, et al. [Effect of stiletto needle intervention combined with massage on dysfunction and pain of knee-joints in patients with knee osteoarthrosis]. Zhen Ci Yan Jiu. 2012 Feb;37(1):59-63, 76. PMID: 22574571.

15. Duivenvoorden T, van Raaij TM, Horemans HL, et al. Do laterally wedged insoles or valgus braces unload the medial compartment of the knee in patients with osteoarthritis? Clin Orthop Relat Res. 2015 Jan;473(1):265-74. doi: 10.1007/s11999-014-3947-5. PMID: 25267266.

16. Eftekharsadat B, Babaei-Ghazani A, Habibzadeh A, et al. Efficacy of action potential simulation and interferential therapy in the rehabilitation of patients with knee osteoarthritis. Ther Adv Musculoskelet Dis. 2015 Jun;7(3):67-75. doi: 10.1177/1759720x15575724. PMID: 26029268.

17. Eyigor S, Karapolat H, Ibisoglu U, et al. [Does transcutaneous electrical nerve stimulation or therapeutic ultrasound increase the effectiveness of exercise for knee osteoarthritis: a randomized controlled study]. Agri. 2008 Jan;20(1):32-40. PMID: 18338277.

18. Fardellone P, Zaim M, Saurel AS, et al. Comparative efficacy and safety study of two chondroitin sulfate preparations from different origin (avian and bovine) in symptomatic osteoarthritis of the knee. Open Rheumatol J. 2013;7:1-12. doi: 10.2174/1874312901307010001. PMID: 23493263.

19. Filardo G, Di Matteo B, Di Martino A, et al. Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Versus Viscosupplementation: A Randomized Controlled Trial. Am J Sports Med. 2015 Jul;43(7):1575-82. doi: 10.1177/0363546515582027. PMID: 25952818.

20. Filardo G, Kon E, Di Martino A, et al. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. BMC Musculoskelet Disord. 2012;13:229. doi: 10.1186/1471-2474-13-229. PMID: 23176112.

21. Filardo G, Kon E, Pereira Ruiz MT, et al. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: single- versus double-spinning approach. Knee Surg Sports Traumatol Arthrosc. 2012 Oct;20(10):2082-91. doi: 10.1007/s00167-011-1837-x. PMID: 22203046.

22. Filardo G, Kon E, Ruiz MTP, et al. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: single- versus double-spinning approach. Knee Surgery Sports Traumatology Arthroscopy. 2012 Oct;20(10):2078-87. PMID: WOS:000308968500028.

23. Forogh B, Mianehsaz E, Shoaee S, et al. Effect of single injection of Platelet-Rich Plasma in comparison with corticosteroid on knee osteoarthritis: a double-blind randomized clinical trial. J Sports Med Phys Fitness. 2015 Jul 14 PMID: 26173792.

24. Forogh B, Mianehsaz E, Shoaee S, et al. Effect of single injection of platelet-rich plasma in comparison with corticosteroid on knee osteoarthritis: a double-blind randomized clinical trial. J Sports Med Phys Fitness. 2016 Jul-Aug;56(7-8):901-8. PMID: 26173792.

25. Fu MY, Zhang ZL. [Knee osteoarthritis treated with acupuncture at the points selected according to syndrome differentiation: a randomized controlled trial]. Zhongguo Zhen Jiu. 2011 Dec;31(12):1062-6. PMID: 22256634.

26. Fu MY, Zhang ZL. Knee osteoarthritis treated with acupuncture based on syndrome differentiation: A randomized controlled trial. World Journal of Acupuncture - Moxibustion. 2012 2012;22(3):11-7. PMID: 2012748632 FULL TEXT LINK http://dx.doi.org/10.1016/S1003-5257(12)60035-X.

27. Gharaibeh A. Plasma rich in platelets versus hyaluronic acid and corticosteroids in the treatment of knee osteoarthritis. Osteoporosis International. 2015 February;26(1 SUPPL. 1):S282.

28. Gobbi A, Lad D, Karnatzikos G. The effects of repeated intra-articular PRP injections on clinical outcomes of early osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc. 2014 Apr 20doi: 10.1007/s00167-014-2987-4. PMID: 24748286.

29. Gobbi A, Lad D, Karnatzikos G. The effects of repeated intra-articular PRP injections on clinical outcomes of early osteoarthritis of the knee. Knee Surgery Sports Traumatology Arthroscopy. 2015 Aug;23(8):2170-7. PMID: WOS:000358375200005.

30. Gokmen F, Akbal A, Komurcu E, et al. Comparison of effects of combined physical therapy program and intra-articular treatment of hyaluronic acid on pain, balance and quality of life in patients with knee osteoarthritis ORIGINAL (NON-ENGLISH) TITLE Diz Osteoartritli Hastalarda Intraartikuler Hyaluronik Asit Tedavisi ile Kombine Fizik Tedavi Uygulamalarinin Anullri, Denge ve Yasam Kalitesi Uzerine Etkisinin Karsilastirilmasi. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi. 2013 April;59 SUPPL. 1:483.

31. Hammad YH, Magid HR, Sobhy MM. Clinical and biochemical study of the comparative efficacy of topical versus oral glucosamine/chondroitin sulfate on osteoarthritis of the knee. Egyptian Rheumatologist. 2015 1;37(2):85-91. PMID: 2015873903 FULL TEXT LINK http://dx.doi.org/10.1016/j.ejr.2014.06.007.

32. Hashemi M, Jalili P, Mennati S, et al. The effects of prolotherapy with hypertonic dextrose versus prolozone (intraarticular ozone) in patients with knee osteoarthritis. Anesthesiology and Pain Medicine. 2015;5(5) PMID: 2015494562 FULL TEXT LINK http://dx.doi.org/10.5812/aapm.27585.

33. Hashemi SM, Madadi F, Razavi S, et al. Intra-articular hyaluronic acid injections Vs. dextrose prolotherapy in the treatment of osteoarthritic knee pain. Tehran University Medical Journal. 2012 May;70(2):119-25. PMID: 2014600481.

34. Hsieh RL, Lee WC. Clinical effects of lateral wedge arch support insoles in knee osteoarthritis: A prospective double-blind randomized study. Medicine. 2016;95(27) PMID: 20160540230 FULL TEXT LINK http://dx.doi.org/10.1097/MD.0000000000003952.

35. Huang J, Zhang W, Lou BD, et al. Observation on clinical efficacy of tension-balance acupuncture therapy in treating knee osteoarthritis. World Journal of Acupuncture - Moxibustion; 2014. p. 42-6.

36. Jo CH, Lee YG, Shin WH, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. Stem Cells. 2014 May;32(5):1254-66. doi: 10.1002/stem.1634. PMID: 24449146.

37. Kalpakcioglu BA, Cakmak B, Bahadir C. Comparison of ultrasound and short wave diathermy therapy in knee osteoarthritis. [Turkish]. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi; 2006. p. 168-73.

38. Kulkarni C, Leena A, Lohit K, et al. A randomized comparative study of safety and efficacy of immediate release glucosamine HCL and glucosamine HCL sustained release formulation in the treatment of knee osteoarthritis: A proof of concept study. J Pharmacol Pharmacother. 2012 Jan;3(1):48-54. doi: 10.4103/0976-500x.92515. PMID: 22368417.

39. Lee HY. [Comparison of effects among Tai-Chi exercise, aquatic exercise, and a self-help program for patients with knee osteoarthritis]. Taehan Kanho Hakhoe chi; 2006. p. 571-80.

40. Luksurapan W, Boonhong J. Effects of phonophoresis of piroxicam and ultrasound on symptomatic knee osteoarthritis. Arch Phys Med Rehabil. 2013 Feb;94(2):250-5. doi: 10.1016/j.apmr.2012.09.025. PMID: 23063790.

41. Lun V, Marsh A, Bray R, et al. Efficacy of Hip Strengthening Exercises Compared With Leg Strengthening Exercises on Knee Pain, Function, and Quality of Life in Patients With Knee Osteoarthritis. Clin J Sport Med. 2015 Nov;25(6):509-17. doi: 10.1097/jsm.0000000000000170. PMID: 25591130.

42. Mascarin NC, Vancini RL, Andrade ML, et al. Effects of kinesiotherapy, ultrasound and electrotherapy in management of bilateral knee osteoarthritis: prospective clinical trial. BMC Musculoskelet Disord. 2012;13:182. doi: 10.1186/1471-2474-13-182. PMID: 22999098.

43. Mehta K, Gala J, Bhasale S, et al. Comparison of glucosamine sulfate and a polyherbal supplement for the relief of osteoarthritis of the knee: A randomized controlled trial [ISRCTN25438351]. BMC Complementary and Alternative Medicine. 2007;7doi: 10.1186/1472-6882-7-34.

44. Mei ZG, Cheng CG, Zheng JF. Observations on curative effect of high-frequency electric sparkle and point-injection therapy on knee osteoarthritis. J Tradit Chin Med. 2011 Dec;31(4):311-5. PMID: 22462237.

45. Melo Mde O, Pompeo KD, Brodt GA, et al. Effects of neuromuscular electrical stimulation and low-level laser therapy on the muscle architecture and functional capacity in elderly patients with knee osteoarthritis: a randomized controlled trial. Clin Rehabil. 2015 Jun;29(6):570-80. doi: 10.1177/0269215514552082. PMID: 25261425.

46. Mirunalini R, Chandrasekaran M, Manimekalai K. Efficacy of chondroitin sulfate with glucosamine versus diacerein in grade ii and iii osteoarthritis knee: A randomized comparative study. Asian Journal of Pharmaceutical and Clinical Research; 2015. p. 42-4.

47. Niazi NS, Niazi SNK, Niazi KNK, et al. Comparison of the effectiveness of knee braces and lateral wedge insole in the management of medial compartment knee osteoarthritis. Pakistan Journal of Medical and Health Sciences. 2014 January-March;8(1):37-40. PMID: 2014311990.

48. Ochiai S, Watanabe A, Oda H, et al. Effectiveness of thermotherapy using a heat and steam generating sheet for cartilage in knee osteoarthritis. J Phys Ther Sci. 2014 Feb;26(2):281-4. doi: 10.1589/jpts.26.281. PMID: 24648649.

49. Odole AC, Ojo OD. A Telephone-based Physiotherapy Intervention for Patients with Osteoarthritis of the Knee. Int J Telerehabil. 2013 Fall;5(2):11-20. doi: 10.5195/ijt.2013.6125. PMID: 25945214.

50. Odole AC, Ojo OD. Is telephysiotherapy an option for improved quality of life in patients with osteoarthritis of the knee? Int J Telemed Appl. 2014;2014:903816. doi: 10.1155/2014/903816. PMID: 24778645.

51. Omori G, Watanabe H, Nawatax A, et al. Efficacy of topical nonsteroidal anti-inflammatory drug (nsaids) adhesive skin patch in quadriceps muscle exercise for knee osteoarthritis - A randomized controlled trial. Osteoarthritis and cartilage; 2013. p. S40.

52. Peungsuwan P, Sermcheep P, Harnmontree P, et al. The Effectiveness of Thai Exercise with Traditional Massage on the Pain, Walking Ability and QOL of Older People with Knee Osteoarthritis: A Randomized Controlled Trial in the Community. J Phys Ther Sci. 2014 Jan;26(1):139-44. doi: 10.1589/jpts.26.139. PMID: 24567694.

53. Provenza JR, Shinjo SK, Silva JM, et al. Combined glucosamine and chondroitin sulfate, once or three times daily, provides clinically relevant analgesia in knee osteoarthritis. Clin Rheumatol. 2014 Aug 3doi: 10.1007/s10067-014-2757-1. PMID: 25085275.

54. Provenza JR, Shinjo SK, Silva JM, et al. Combined glucosamine and chondroitin sulfate, once of three times daily, provide clinically relevant analgesia in knee osteoarthritis. Arthritis and Rheumatism. 2012 October;64 SUPPL. 10:S487.

55. Rabini A, Piazzini DB, Tancredi G, et al. Deep heating therapy via microwave diathermy relieves pain and improves physical function in patients with knee osteoarthritis: a double-blind randomized clinical trial. Eur J Phys Rehabil Med. 2012 Dec;48(4):549-59. PMID: 22820824.

56. Raeissadat SA, Rayegani SM, Hassanabadi H, et al. Knee Osteoarthritis Injection Choices: Platelet- Rich Plasma (PRP) Versus Hyaluronic Acid (A one-year randomized clinical trial). Clin Med Insights Arthritis Musculoskelet Disord. 2015;8:1-8. doi: 10.4137/cmamd.s17894. PMID: 25624776.

57. Rahimzadeh P, Imani F, Faiz SH, et al. Investigation the efficacy of intra-articular prolotherapy with erythropoietin and dextrose and intra-articular pulsed radiofrequency on pain level reduction and range of motion improvement in primary osteoarthritis of knee. J Res Med Sci. 2014 Aug;19(8):696-702. PMID: 25422652.

58. Richards JD, Sanchez-Ballester J, Jones RK, et al. A comparison of knee braces during walking for the treatment of osteoarthritis of the medial compartment of the knee. J Bone Joint Surg Br. 2005 Jul;87(7):937-9. doi: 10.1302/0301-620X.87B7.16005. PMID: 15972906.

59. Saleki M, Ahadi T, Razi M, et al. Comparison of the effects of acupuncture and physical modality on symptoms of knee osteoarthritis. [Persian]. Journal of Isfahan Medical School; 2012.

60. Sarsan A, Akkaya N, Ozgen M, et al. Comparing the efficacy of mature mud pack and hot pack treatments for knee osteoarthritis. J Back Musculoskelet Rehabil. 2012;25(3):193-9. doi: 10.3233/bmr-2012-0327. PMID: 22935858.

61. Say F, Gurler D, Yener K, et al. Platelet-rich plasma injection is more effective than hyaluronic acid in the treatment of knee osteoarthritis. Acta Chir Orthop Traumatol Cech. 2013;80(4):278-83. PMID: 24119476.

62. Say F, GÜRler D, Yener K, et al. Platelet-rich plasma injection is more effective than hyaluronic acid in the treatment of knee osteoarthritis. Acta Chirurgiae Orthopaedicae et Traumatologiae Cechoslovaca. 2013;80(4):278-83.

63. Spakova T, Rosocha J, Lacko M, et al. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. Am J Phys Med Rehabil. 2012 May;91(5):411-7. doi: 10.1097/PHM.0b013e3182aab72. PMID: 22513879.

64. Spaková T, Rosocha J, Lacko M, et al. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. American Journal of Physical Medicine and Rehabilitation. 2012;91(5):411-7. doi: 10.1097/PHM.0b013e3182aab72.

65. Teslim OA, Adebowale AC, Ojoawo AO, et al. Comparative effects of pulsed and continuous short wave diathermy on pain and selected physiological parameters among subjects with chronic knee osteoarthritis. Technol Health Care. 2013;21(5):433-40. doi: 10.3233/thc-130744. PMID: 24004650.

66. van Raaij TM, Reijman M, Brouwer RW, et al. Medial knee osteoarthritis treated by insoles or braces: a randomized trial. Clinical orthopaedics and related research; 2010. p. 1926-32.

67. Vaquerizo V, Plasencia MA, Arribas I, et al. Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: a randomized controlled trial. Arthroscopy. 2013 Oct;29(10):1635-43. doi: 10.1016/j.arthro.2013.07.264. PMID: 24075613.

68. Vega A, Martin-Ferrero MA, Del Canto F, et al. Treatment of Knee Osteoarthritis With Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial. Transplantation. 2015 Mar 27doi: 10.1097/tp.0000000000000678. PMID: 25822648.

69. Wang JL, Chai CH, Xu YM. [Clinical observations on the effect of Tuigua manipulation combined with quadriceps exercise for the treatment of degenerative gonarthritis]. Zhongguo gu shang [China journal of orthopaedics and traumatology]; 2008. p. 887-9.

70. Wangroongsub Y, Tanavalee A, Wilairatana V, et al. Comparable clinical outcomes between glucosamine sulfate-potassium chloride and glucosamine sulfate sodium chloride in patients with mild and moderate knee osteoarthritis: a randomized, double-blind study. J Med Assoc Thai. 2010 Jul;93(7):805-11. PMID: 20649060.

No usable data – N = 80

1. Abbott JH, Fitzgerald G, Fritz JM, et al. Do manual therapy or booster sessions in addition to exercise therapy for knee osteoarthritis provide additional benefits? a randomized clinical trial. Osteoarthritis and cartilage; 2015. p. A385.

2. Abbott JH, Robertson MC, Chapple C, et al. Manual therapy, exercise therapy, or both, in addition to usual care, for osteoarthritis of the hip or knee: a randomized controlled trial. 1: clinical effectiveness. Osteoarthritis Cartilage. 2013 Apr;21(4):525-34. doi: 10.1016/j.joca.2012.12.014. PMID: 23313532.

3. Alpayci M, Hiz O, Ediz L, et al. The effect of traction in the treatment of knee osteoarthritis: A prospective randomized controlled trial, Diz osteoartritinde traksiyon tedavisinin etkisi: Prospektif randomize kontrollu califlma. [Turkish, English]. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi; 2011. p. 259.

4. Barry HC. Dextrose prolotherapy decreases pain and stiffness in knee degenerative joint disease. American Family Physician. 2013;88(9) PMID: 2013716323.

5. Bighea AC, Patru S, Marcu IR, et al. The effectiveness of combined exercises and therapeutic ultrasound to patients with knee osteoarthritis. Annals of the rheumatic diseases; 2013.

6. Birsan SD, Cioara F. Study over phonophoresis with capsaicin in knee osteoarthritis. Osteoporosis International. 2014 April;25 SUPPL. 2:S413.

7. Bliddal H, Christensen P, Bartels EM, et al. Long-term intervention with weight loss in patients with concomitant obesity and knee osteoarthritis: A randomised trial (the light study). Annals of the rheumatic diseases; 2014.

8. Boyaci A, Tutotlu A, Boyaci N, et al. Comparison of the efficacy of ketoprofen phonophoresis, ultrasound and short-wave diathermy in knee osteoarthritis, Diz Osteoartritinde Ketoprofen Fonoforezi, Ultrason ve Kisa Dalga Diaterminin Etkinlitinin Karsilastirilmasi. [Turkish, English]. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi; 2013. p. 353.

9. Calis FA, Durmaz B, Baydar M, et al. The effectiveness of TENS, interferential current and short-wave diathermy on knee osteoarthritis: Multicenter, randomized, placebo controlled clinical study, Diz osteoartritinde TENS, interferansiyel akim ve kisa dalga diaterminin etkinliti: Cok merkezli, randomize, plasebo kontrollu klinik califlma. [Turkish, English]. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi; 2011. p. 141.

10. Callaghan M, Parkes MJ, Forsythe LM, et al. Beneficial effects of a brace for patellofemoral oa: Results of a randomised trial. Osteoarthritis and cartilage; 2013. p. S23.

11. Castgillo JR, Hochberg MC, Martel-Pelletier J, et al. Combined chondroitin sulfate and Glucosamine versus celecoxib for painful Knee osteoarthritis: Post-hoc analyses by Kellgren and

Lawrence grade and C-reactive protein level from a randomized, double-blind, multicentre clinical trial. Clinical Therapeutics. 2015 August;37(8 SUPPL. 1):e122.

12. Cheung C, Wyman J, Resnick B. Is yoga effective for knee osteoarthritis in older women? Osteoarthritis and cartilage; 2012. p. S280.

13. Christensen R, Leeds AR, Lohmander S, et al. Efficacy of dieting or exercise vs. control in obese knee osteoarthritis patients after a clinically significant weight loss: A pragmatic randomized controlled trial. Osteoarthritis and Cartilage. Conference: 2010 Osteoarthritis Research Society International, OARSI World Congress Brussels Belgium. Conference Start: 20100923 Conference End: 20100926. Conference Publication: (var.pagings); 2010. p. S143-s4.

14. Chung M, Wong JB, Chang S, et al. Nutraceutical Products and Pain or Non-Pain Medications Use in Patients with Knee Osteoarthritis [abstract]. 2014 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2014;66 (suppl S10):S110.

15. Cioara F, Birsan SD, Vicas L, et al. Balneary physical kinetic therapy effects over gonarthrosis symptoms. Osteoporosis International. 2014 April;25 SUPPL. 2:S409-S10.

16. Coleman S, Briffa NK, Carroll G, et al. An osteoarthritis of the knee self-management education program delivered by multidisciplinary health professionals; A randomised controlled trial. Physiotherapy (United Kingdom); 2011. p. eS1457.

17. Davis A, Palaganas M, Li L. Support for Community-Based Programs for Managing Hip and Knee Osteoarthritis: Results of a Public Survey [abstract]. 2015 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2015;67 (suppl 10):1194.

18. Duivenvoorden T, Raaij T, Horemans H, et al. Do laterally wedged insoles and valgus knee braces really unload the medial compartment of the knee? Results of a RCT. Osteoarthritis and cartilage; 2014. p. S455-s6.

19. Farias FE, Silva CA, Cernigoy CH, et al. Analysis and correlation of physical therapy tests, pain, function and quality of life questionnaires in patients from parqve (project arhtritis recovering quality of life by means of education). Osteoarthritis and cartilage; 2015. p. A167.

20. Fary R, Carroll GJ, Briffa TG, et al. Is pulsed electrical stimulation a viable treatment option in managing pain from osteoarthritis of the knee? Physiotherapy (United Kingdom); 2011. p. eS325-eS6.

21. Filipovic K, Subin-Teodosijevic S, Zvekic-Svorcan J, et al. Symptomatic effect crystalline glucosamine sulfate osteoarthritis of the knee. Osteoporosis International. 2015 February;26(1 SUPPL. 1):S319.

22. Filipović K, Subin-Teodosijevic S, Zvekić-Svorcan J, et al. Symptomatic effect crystalline glucosamine sulfate osteoarthritis of the knee. Osteoporosis International. 2015 February;26(1 SUPPL. 1):S319.

23. Fitzgerald GK, Fritz J, Childs J, et al. Exercise, Manual Therapy, and Use of Booster Sessions in Physical Therapy for Knee OA: A Multi-Center Randomized Clinical Trial [abstract]. 2014 ACR/ARHP Annual Meeting. Arthritis rheumatol. 2014;66 (suppl S10):S393.

24. Forrester K, Taufiq F, Samuels J. Comparison of Knee Osteoarthritis Treatment in the Non-Obese Versus Obese Populations Across Different Medical Specialties [abstract]. . Arthritis Rheumatol. 2015;67(suppl 10).

25. Foster NE. Management of primary care for people with knee osteoarthritis: The beep study (best evidence for exercise in knee pain). Annals of the rheumatic diseases; 2013.

26. Goldenstein-Schainberg C, Fuller R, Matias A, et al. Effectiveness of long-term use of minimalist footwear on pain and function in knee osteoarthritis. Osteoporosis international; 2013. p. S139.

27. Gomiero AB, Trevisani VM, Kayo AH, et al. Sensorimotor training versus resistance training in patients with knee osteoarthritis. Arthritis and rheumatism; 2011.

28. Gudbergsen H, Boesen M, Lohmander LS, et al. Weight loss is effective for symptomatic relief in obese subjects with knee osteoarthritis independently of joint damage severity assessed by high-field MRI and radiography. Osteoarthritis Cartilage. 2012 Jun;20(6):495-502. doi: 10.1016/j.joca.2012.02.639. PMID: 22401872.

29. Henriksen M, Christensen R, Danneskiold-Samsoe B, et al. Changes in knee muscle strength and muscle mass after weight loss in obese patients with knee osteoarthritis: A prospective cohort study. Osteoarthritis and cartilage; 2011. p. S211.

30. Hochberg MC, Lao L, Langenberg P, et al. Efficacy and Safety of the Chinese Herbal Compound Hou-Lou-Xiao-Ling Dan in Patients with Osteoarthritis of the Knee: Results of a Phase II International Study [abstract]. 2012 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2012;64 (suppl S10):S112.

31. Hochberg MC, Peng L, Ahl J, et al. Duloxetine as treatment for knee pain in patients with osteoarthritis who regularly use nonsteroidal anti-inflammatory drugs (NSAIDS): A post hoc analysis of two randomized, placebo-controlled trials. Osteoarthritis and Cartilage. 2011 September;19 SUPPL. 1:S146-S7.

32. Huang H, Ologhobo T, Jin V, et al. The Effectiveness of Low-Impact Exercise Program on Musculoskeletal Health of Asian Older Adults [abstract]. 2015 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2015;67 (suppl 10):1193.

33. Hurley M, Dickson K, Hauari H, et al. People's Views, Beliefs and Experiences of Exercise for Chronic Hip and Knee Pain: Cochrane Review with Qualitative Synthesis. 2014 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2014;66 (suppl S10):S1017.

34. Hussein N, Saad M, El Sawey N. Effect of combined balance and isotonic resistive exercises versus isotonic resistive exercise alone on proprioception and stabilizing reactions of quadriceps and hamstrings and functional capacity of knee osteoarthritis patients. 8th Mediterranean Congress of Physical and Rehabilitation Medicine. 2010:91-106. PMID: WOS:000325362300015.

35. Jeremic M. Therapeutic effect viscosuplementa and local infiltration of corticosteroid in patients with knee osteoarthritis. Osteoporosis International. 2014 April;25 SUPPL. 2:S433.

36. Kaya Mutlu E, Razak Ozdincler A, Ercin E. Comparison of two different mobilization techniques in the management of osteoarthritis of the knee: A randomized clinical trial. Osteoarthritis and cartilage; 2015. p. A391-a2.

37. Kilinc S, Kabayel DD, Ozdemir F, et al. Comparison of the effectiveness of isometric and isokinetic exercise in patients with osteoarthritis of knee, Gonartrozlu Hastalarda Izometrik ve Izokinetik Egzersizlerin Etkinlitinin Karsilastirilmasi. [Turkish, English]. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi; 2013. p. 344.

38. Knoop J, Leeden M, Roorda LD, et al. Importance of adherence in outcome of exercise therapy in patients with knee osteoarthritis. Osteoarthritis and cartilage; 2014. p. S458-s9.

39. Kon E, Filardo G, Di Martino A, et al. Platelet-rich plasma intra-articular injections versus visco-supplementation as a treatment for early osteoarthritis: A randomized double blind study. Journal of Orthopaedics and Traumatology. 2013 October;14(1 SUPPL. 1):S64-S5.

40. Kou U, Tohyama H, Chiba T, et al. Long-term effects of video-based home exercise on clinical and radiographic outcomes in subject with knee osteoarthritis: A two-year randomized controlled trial. Osteoarthritis and cartilage; 2013. p. S40.

41. Li LW, Harris RE, Murphy SL, et al. Feasibility of a Randomized Controlled Trial of Self-Administered Acupressure for Symptom Management in Older Adults with Knee Osteoarthritis. Journal of Alternative and Complementary Medicine. 2016 1;22(5):396-403. PMID: 20160378951 FULL TEXT LINK http://dx.doi.org/10.1089/acm.2015.0231.

42. March L, Hunter D, Ward C, et al. A randomised placebo controlled pilot study of autologous non-expanded adipose-derived mesenchymal stem cells in the treatment of knee osteoarthritis. Internal Medicine Journal. 2013 May;43 SUPPL. 2:4-5.

43. Mathur S, Saracoglu M, Kuroda M, et al. Functional testing and pre-to post pain measure outcomes in chronic knee osteoarthritis pain with milnacipran: Interim analysis of a randomized, double-blind, placebo-controlled trial. Journal of Pain. 2013 April;14(4 SUPPL. 1):S66.

44. Mills KAG, Naylor JM, Eyles JP, et al. Examining the minimal important difference of patient-reported outcome measures for individuals with knee osteoarthritis: A model using the knee injury and osteoarthritis outcome score. Journal of Rheumatology. 2016 1;43(2):395-404. PMID: 20160100941 FULL TEXT LINK http://dx.doi.org/10.3899/jrheum.150398.

45. Moen M, Weir A, Bakker E, et al. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: An updated systematic review and meta-analysis. Osteoarthritis and Cartilage. 2016 April;24 SUPPL. 1:S520-S1.

46. Multanen J, Hakkinen A, Kujala U, et al. The effects of bone exercise on knee pain, stiffness and function among women with mild knee osteoarthritis: Randomized, controlled trial. Physiotherapy (United Kingdom); 2011. p. eS852-eS3.

47. National Institute for Health and Care Excellence. Osteoarthritis: national clinical guideline for care and management in adults Royal College of Physicians. 2014.

48. Oida Y, Morozumi K, Nakamura N, et al. [Effectiveness of a community health service program using exercise intervention for elderly people with osteoarthritis of the knees: a randomized controlled trial]. [Nihon k?sh? eisei zasshi] Japanese journal of public health; 2008. p. 228-37.

49. Ozgen M, Mehmetotlu O, Armatan O. Efficiency of local diclophenac treatment in knee osteoartritis, Diz osteoartritinde lokal diklofenak tedavisinin etkinliti. [Turkish, English]. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi; 2011. p. 299.

50. Paterson K, Nicholls M, Bates D. Intra-articular injection of platelet-rich plasma in patients with knee osteoarthritis: A randomised controlled pilot study. Journal of Science and Medicine in Sport. 2013 December;16 SUPPL. 1:e90.

51. Peter WFH, Hurkmans E, van der Wees P, et al. Quality Indicators For Physical Therapy Management In Hip and Knee Osteoarthritis and Rheumatoid Arthritis [abstract]. 2013 ACR/ARHP Annual Meeting. 2013.

52. Povoroznyuk V, Grygorieva N, Unusova S, et al. Effectiveness of exercise therapy in combination with glucosamine and chondroitin treatment in postmenopausal women with knee osteoarthritis. European Journal of Pain Supplements. 2011 September;5(1):185.

53. Prieto-Alhambra D, Morros R. Use of Drug Combinations in Patients with Osteoarthritis: A Population-Based Cohort Study [abstract]. 2012 ACR/ARHP Annual Meeting. Arthritis rheumatol 2012;64 (suppl S10):S117-8.

54. Rahela MI, Patru S, Bighea A, et al. Efficacy of physical exercice in patients with knee osteoarthritis. Annals of the Rheumatic Disease; 2013.

55. Reinhardt JD, Pu W, Yang L, et al. Effects of whole body vibration exercise associated with quadriceps resistance exercise on functioning and quality of life in patients with knee osteoarthritis: A randomized controlled trial. PM and R; 2014. p. S95-s6.

56. Rillo OL, Riera H, Espinosa-Morales R, et al. Panlar Consensus on Hand, Hip and Knee OA [abstract]. 2015 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2015;67 (suppl 10):1497.

57. Roper JA, Bressel E, Tillman MD. Acute aquatic treadmill exercise improves gait and pain in people with knee osteoarthritis. Arch Phys Med Rehabil. 2013 Mar;94(3):419-25. doi: 10.1016/j.apmr.2012.10.027. PMID: 23131526.

58. Saygi EK, Ozcan EE, Sanal C, et al. Effects of prolotherapy with 10% dextrose and oral glucosamine sulfate on the postural stability among the patients with knee osteoarthritis ORIGINAL (NON-ENGLISH) TITLE Diz Osteoartriti Tanili Hastalarda %10 Dekstroz Ile Proloterapi ve Glukozamin Sulfat Uygulamalarinin Postural Stabilite Uzerine Etkileri. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi. 2013 April;59 SUPPL. 1:251.

59. Schmidt S. Uncontrolled clinical study of the efficacy of ambulant fasting in patients with osteoarthritis∗. European Journal of Integrative Medicine. 2010 December;2(4):239.

60. Segal NA, Glass NA, Teran-Yengle P, et al. Intensive Gait Training for Older Adults with Symptomatic Knee Osteoarthritis. Am J Phys Med Rehabil. 2015 Oct;94(10 Suppl 1):848-58. doi: 10.1097/phm.0000000000000264. PMID: 25768068.

61. Segal NA, Yack HJ, Glass NA, et al. Intensive gait training improves pain and mobility in older adults with symptomatic knee osteoarthritis. Journal of the American Geriatrics Society; 2010. p. S130.

62. Shakoor MA, Rahman MS, Azad AK, et al. Effects of isometric quadriceps muscle strengthening exercise on chronic osteoarthritis of the knee. Bangladesh Med Res Counc Bull. 2010 Apr;36(1):20-2. PMID: 21280554.

63. Skou ST, Roos E, Simonsen O, et al. The combined efficacy of multimodal non-surgical treatment on pain and sensitization in patients with knee osteoarthritis not eligible for a total knee arthroplasty-an ancillary analysis from a randomized controlled trial. Osteoarthritis and Cartilage. 2015 April;23 SUPPL. 2:A34-A5.

64. Smith SR, Katz JN, Collins JE, et al. Cost-Effectiveness of Opioids for the Treatment of Knee Osteoarthritis: Impact of Chronic Opioid Use on Total Knee Arthroplasty Outcomes [abstract]. Arthritis Rheumatol. 2015;67(suppl 10).

65. Sriram S, Ramesh R, Saravanan M, et al. Intra articular platelet rich plasma versus intra articular steroids versus viscosupplementation in the management of primary osteoarthritis of knee. International Journal of Rheumatic Diseases. 2015 September;18 SUPPL. 1:81-2.

66. Srivastava RN, Avasthi V, Srivastava SR, et al. Does yoga improve pain, stiffness and physical disability in knee osteoarthritis?-A randomize controlled clinical trial. Osteoarthritis and Cartilage. 2015 April;23 SUPPL. 2:A167.

67. Strebkova E, Solovyeva I, Sharapova E, et al. Evaluation of treatment efficacy of orlistat in obese women with knee osteoarthritis. Osteoporosis International. 2014 April;25 SUPPL. 2:S353.

68. Tetreault P, Baliki M, Vachon-Presseau E, et al. Cortical Reorganization after Duloxetine Treatment-Related Pain Decrease in Knee Osteoarthritis [abstract]. 2014 ACR/ARHP Annual Meeting. Arthritis rheumatol. 2014;66 (suppl S10):S410-1.

69. Tohyama H, Chiba T, Kou U, et al. Effects of video-based home exercise on clinical and radiographic outcomes in adults with knee osteoarthritis: A one-year randomized controlled trial. Osteoarthritis and cartilage; 2011. p. S37.

70. Villadsen A, Overgaard S, Christensen R, et al. Neuromuscular exercise (NEMEX-TJR) improves knee extension muscle power and chair stands ability in patients with severe knee osteoarthritis compared to controls: A randomized controlled trial. Osteoarthritis and cartilage; 2012. p. S266.

71. Wilder E, Lin J, Bomfim F, et al. Reduction of Treatment Needed for Knee Osteoarthritis after Bariatric Surgery [abstract]. 2015 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2015;67 (suppl 10):322.

72. Yamada E, Rodrigues PL, Almeida FR, et al. Effectiveness of transcutaneous electrical nerve stimulation, therapeutic exercise and the pursuit of the association of two techniques in knee osteoarthritis. Physiotherapy. 2011 June;(2011) 97 SUPPL. 1:eS1051-eS2.

73. Yang S, Eaton CB, McAlindon T, et al. Long-term effectiveness of glucosamine and chondroitin in treating knee osteoarthritis: An analysis with marginal structural modeling. Osteoarthritis and Cartilage. 2014 April;22 SUPPL. 1:S203.

74. Yavuz M, Ataotlu S, Ozsahin M. Comparison of isokinetic exercise with treatments of laser and iontophoresis for patients with osteoarthritis of the knee, Diz osteoartriti olan hastalarda izokinetik egzersiz ile lazer ve iyontoforez tedavilerinin karflilafltirilmasi. [Turkish, English]. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi; 2011. p. 297.

75. Yesilyurt H, Tastekin N, Hakguder AH, et al. A comparison study of the clinical efficacy of ketoprophen phonophoresis and ultrasound therapy in primary knee osteoarthritis, Primer diz osteoartriinde ketoprofen fonoforezi ve ultrason tedavilerinin klinik etkinlitinin karflilafltirilmasi. [Turkish, English]. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi; 2011. p. 259.

76. Yildirim MA, Ucar D, Ones K, et al. Comparison of the duration of therapeutic ultrasound in patients with knee osteoarthritis. Annals of the rheumatic diseases; 2014.

77. Yildiz SK, Silte AD, Kaysin MY, et al. Effectiveness of ultrasound therapy in knee osteoarthritis, Diz Osteoartritli Hastalarda Ultrason Tedavisinin Etkinliti. [Turkish, English]. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi; 2013. p. 335.

78. Zeng C, Wei J, Lei G-H. Is chondroitin sulfate plus glucosamine superior to placebo in the treatment of knee osteoarthritis? Annals of the rheumatic diseases; 2015. p. e37.

79. Zhang Y, Shen CL, Brismee JM, et al. Exploring the effects of self-managed acupressure on pain, function and osteoarthritis biomarkers among postmenopausal women with osteoarthritic knee pain: A feasibility study. Journal of alternative and complementary medicine (New York, N.Y.); 2013. p. A31.

80. Zhao L, Wu F, Wang L, et al. Effectiveness of moxibustion treatment as adjunctive therapy in osteoarthritis of the knee: A randomized controlled clinical trial. Journal of alternative and complementary medicine (New York, N.Y.); 2013. p. A6.

Multi-component interventions – N = 27

1. Allen KD, Bongiorni D, Bosworth HB, et al. Randomized Clinical Trial of Group Vs. Individual Physical Therapy for Knee Osteoarthritis [abstract]. 2014;2014 ACR/ARHP Annual Meeting

2. Arazpour M, Bani MA, Maleki M, et al. Comparison of the efficacy of laterally wedged insoles and bespoke unloader knee orthoses in treating medial compartment knee osteoarthritis. Prosthet Orthot Int. 2013 Feb;37(1):50-7. doi: 10.1177/0309364612447094. PMID: 22864510.

3. Arti HR, Azemi ME. Comparing the effect of Glucosamine and Glucosamine With Alendronate in Symptomatic Relieve of Degenerative Knee Joint Disease: A Double- blind Randomized Clinical Trial Study. Jundishapur J Nat Pharm Prod. 2012 Summer;7(3):87-92. PMID: 24624161.

4. Bennell K, Wrigley T, Kyriakides M, et al. Comparison of neuromuscular and quadriceps strengthening exercise in people with medial knee osteoarthritis and varus malalignment: Randomised controlled trial. Osteoarthritis and cartilage; 2013. p. S273-s4.

5. Bennell KL, Kyriakides M, Hodges PW, et al. Effects of two physiotherapy booster sessions on outcomes with home exercise in people with knee osteoarthritis: a randomized controlled trial. Arthritis Care Res (Hoboken). 2014 Nov;66(11):1680-7. doi: 10.1002/acr.22350. PMID: 24757032.

6. Brito Sr NL, Rezende MU, Campos GC, et al. Analysis of anthropometric measurements and dietary intake in patients undergoing a multi-professional program osteoarthritis treatment (parqve-project arhtritis recovering quality of life by means of education). Osteoarthritis and cartilage; 2015. p. A386-a7.

7. Choi YL, Kim BK, Hwang YP, et al. Effects of isometric exercise using biofeedback on maximum voluntary isometric contraction, pain, and muscle thickness in patients with knee osteoarthritis. J Phys Ther Sci. 2015 Jan;27(1):149-53. doi: 10.1589/jpts.27.149. PMID: 25642061.

8. Ebnezar J, Nagarathna R, Bali Y, et al. Effect of an integrated approach of yoga therapy on quality of life in osteoarthritis of the knee joint: A randomized control study. Int J Yoga. 2011 Jul;4(2):55-63. doi: 10.4103/0973-6131.85486. PMID: 22022123.

9. Ebnezar J, Nagarathna R, Yogitha B, et al. Effect of integrated yoga therapy on pain, morning stiffness and anxiety in osteoarthritis of the knee joint: A randomized control study. Int J Yoga. 2012 Jan;5(1):28-36. doi: 10.4103/0973-6131.91708. PMID: 22346063.

10. Ebnezar J, Nagarathna R, Yogitha B, et al. Effects of an integrated approach of hatha yoga therapy on functional disability, pain, and flexibility in osteoarthritis of the knee joint: a randomized controlled study. J Altern Complement Med. 2012 May;18(5):463-72. doi: 10.1089/acm.2010.0320. PMID: 22537508.

11. Espejo Antúnez L, Cardero Durán M, Caro Puértolas B, et al. [Effects of exercise on the function and quality of life in the institutionalised elderly diagnosed with gonarthrosis]. Revista española de geriatría y gerontología; 2012. p. 262-5.

12. Fazaa A, Souabni L, Ben Abdelghani K, et al. Comparison of the clinical effectiveness of thermal cure and rehabilitation in knee osteoarthritis. A randomized therapeutic trial. Ann Phys Rehabil Med. 2014 Dec;57(9-10):561-9. doi: 10.1016/j.rehab.2014.09.007. PMID: 25447748.

13. Hunter D, Gross KD, McCree P, et al. Realignment treatment for medial tibiofemoral osteoarthritis: randomised trial. Ann Rheum Dis. 2012 Oct;71(10):1658-65. doi: 10.1136/annrheumdis-2011-200728. PMID: 22377805.

14. Kocaman O, Koyuncu H, Dinc A, et al. The comparison of the effects of electrical stimulation and exercise in the treatment of knee osteoarthritis. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi; 2008. p. 54-8.

15. Kudo M, Watanabe K, Otsubo H, et al. Analysis of effectiveness of therapeutic exercise for knee osteoarthritis and possible factors affecting outcome. J Orthop Sci. 2013 Nov;18(6):932-9. doi: 10.1007/s00776-013-0443-9. PMID: 24085378.

16. Massari F, De Carvalho VA, Da Silva CR. Efficacy and safety of the association of glucosamine sulfate and chondroitin sulfate in the treatment of symptomatic knee osteoarthritis ORIGINAL (NON-ENGLISH) TITLE Eficacia e seguranca da associacao de sulfato de glucosamina e sulfato de condroitina no tratamento sintomatico da osteoartrite de joelho. Revista Brasileira de Medicina. 2014;71:6-7. PMID: 2014546850.

17. Matei D, Bighea A, Patru S, et al. The place of kinetotherapy in rehabilitation program of knee osteoarthritis patients. Osteoporosis International. 2014 April;25 SUPPL. 2:S279.

18. Müller-Rath R, Cho HY, Siebert CH, et al. [Clinical and gait analytical investigation of valgus knee bracing in therapy for medial degenerative joint disease of the knee]. Zeitschrift für Orthopädie und Unfallchirurgie; 2011. p. 160-5.

19. Nunez M, Nunez E, Segur JM, et al. The effect of an educational program to improve health-related quality of life in patients with osteoarthritis on waiting list for total knee replacement: a randomized study. Osteoarthritis Cartilage. 2006 Mar;14(3):279-85. doi: 10.1016/j.joca.2005.10.002. PMID: 16309929.

20. Rafiaee M, Karimi MT. The effects of various kinds of lateral wedge insoles on performance of individuals with knee joint osteoarthritis. Int J Prev Med. 2012 Oct;3(10):693-8. PMID: 23112895.

21. Salli A, Ugurlu H, Emlik D. Comparison of the effectiveness of concentric, combined concentric-eccentric and isometric exercises on symptoms and functional capacity in patients with knee osteoarthritis. [Turkish]. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi; 2006. p. 61-7.

22. Saraboon Y, Aree-Ue S, Maruo SJ. The Effect of Multifactorial Intervention Programs on Health Behavior and Symptom Control Among Community-Dwelling Overweight Older Adults With Knee Osteoarthritis. Orthop Nurs. 2015 Sep-Oct;34(5):296-308. doi: 10.1097/nor.0000000000000180. PMID: 26375841.

23. Shirokova LY, Noskov SM, Abrosimova EB, et al. [Effect of local therapy of autolgous platelet-enriched plasma on pain syndrome in patients with knee osteoarthritis]. Klinicheskaia meditsina. 2012;90(10):48-52.

24. Skou ST, Rasmussen S, Laursen MB, et al. The efficacy of 12 weeks non-surgical treatment for patients not eligible for total knee replacement: a randomized controlled trial with 1-year follow-up. Osteoarthritis Cartilage. 2015 Sep;23(9):1465-75. doi: 10.1016/j.joca.2015.04.021. PMID: 25937024.

25. Tefner IK, Gaal R, Koroknai A, et al. The effect of Neydharting mud-pack therapy on knee osteoarthritis: a randomized, controlled, double-blind follow-up pilot study. Rheumatol Int. 2013 Oct;33(10):2569-76. doi: 10.1007/s00296-013-2776-2. PMID: 23689969.

26. Wu SF, Kao MJ, Wu MP, et al. Effects of an osteoarthritis self-management programme. J Adv Nurs. 2011 Jul;67(7):1491-501. doi: 10.1111/j.1365-2648.2010.05603.x. PMID: 21375573.

27. Zotkin EG, Kharitonova TV, Shkireeva S. [Clinical use of chondroitin sulfate in patients with osteoarthritis in geriatric practice]. Adv Gerontol. 2014;27(2):366-75. PMID: 25306673.

Duplicate or duplicate data – N = 39

1. Atukorala I, Makovey J, Lawler L, et al. Is there a dose response relationship between weight loss and symptom improvement in persons with symptomatic knee osteoarthritis? Osteoarthritis and Cartilage. 2014 April;22 SUPPL. 1:S50-S1.

2. Bennell K, Ahamed Y, Bryant C, et al. Physiotherapist-delivered exercise and pain coping skills training is more effective than either intervention alone in knee osteoarthritis. Journal of science and medicine in sport; 2013. p. e91.

3. Bennell KL, Ahamed Y, Bryant C, et al. Physiotherapist-delivered exercise and pain coping skills training is more effective than either intervention alone in knee osteoarthritis. Osteoarthritis and cartilage; 2014. p. S192-s3.

4. Bennell KL, Ahamed Y, Jull G, et al. Physical Therapist-Delivered Pain Coping Skills Training and Exercise for Knee Osteoarthritis: Randomized Controlled Trial. Arthritis Care Res (Hoboken). 2016 May;68(5):590-602. doi: 10.1002/acr.22744. PMID: 26417720.

5. Bove A, Smith K, Bise C, et al. What Is the Most Cost-Effective Physical Therapy Strategy to Treat Knee Osteoarthritis? [abstract]. Arthritis Rheumatol. 2015;67(suppl 10).

6. Bruyere O, Pavelka K, Rovati LC, et al. Total joint replacement after glucosamine sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients from two previous 3-year, randomised, placebo-controlled trials. Osteoarthritis and Cartilage. 2008;16(2):254-60. doi: 10.1016/j.joca.2007.06.011.

7. Cho Sr JJ, Kim TW, Park YM, et al. Tissuegene-C (TG-C) in patients with osteoarthritis: A phase iib clinical study. Osteoarthritis and Cartilage. 2013 April;21 SUPPL. 1:S147.

8. Crossley K, Vicenzino B, Pandy M, et al. A randomised clinical trial of targeted physiotherapy for patellofemoral osteoarthritis. Journal of science and medicine in sport; 2012. p. S245.

9. Douidi-Hamimed FZ, Mekaouche M, Derdour S, et al. Functional and clinical outcome after self-management in people with knee osteoarthritis. Annals of Physical and Rehabilitation Medicine. 2013 October;56 SUPPL. 1:e362.

10. Felson DT, Parkes MJ, Gait AD, et al. A randomised trial of a brace for patellofemoral osteoarthritis targeting knee pain and bone marrow lesions. Arthritis and rheumatism; 2013. p. S717.

11. Fransen M, Agaliotis M. Glucosamine and chondroitin for knee osteoarthritis: a double-blind randomised placebo-controlled clinical trial evaluating single and combination regimens. 2015 May;74(5):851-8. doi: 10.1136/annrheumdis-2013-203954. PMID: 24395557.

12. Fransen M, Agaliotis M, Nairn L, et al. Glucosamine and chondroitin for knee osteoarthritis: A double-blind randomised placebo-controlled clinical trial evaluating single and combination regimens. Annals of the rheumatic diseases; 2015. p. 851-8.

13. Fransen M, Agaliotis M, Nairn L, et al. Glucosamine and chondroitin for knee osteoarthritis: A double blind randomised controlled clinical trial evaluating single and combination regimens. Osteoarthritis and Cartilage. 2014 April;22 SUPPL. 1:S457.

14. Henriksen M, Klokker L, Graven-Nielsen T, et al. Exercise Therapy Reduces Pain Sensitivity In Patients With Knee Osteoarthritis: A Randomized Controlled Trial [abstract]. 2013 ACR/ARHP Annual Meeting. Arthritis Rheumatol. 2013;65 (suppl S10):S775.

15. Hochberg M, Martel-Pelletier J, Monfort J, et al. Combined chondroitin sulfate and glucosamine is comparable to celecoxib for painful knee osteoarthritis. Results from a multicenter, randomized, double-blind, phase IV non-inferiority trial. Arthritis and Rheumatology. 2014 October;66 SUPPL. 10:S971.

16. Hochberg MC, Martel-Pelletier J, Monfort J, et al. Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. Ann Rheum Dis. 2016 Jan;75(1):37-44. doi: 10.1136/annrheumdis-2014-206792. PMID: 25589511.

17. Hochberg MC, Martel-Pelletier J, Monfort J, et al. Multicentric osteoarthritis intervention study with sysadoa (MOVES): Effects of combined glucosamine hydrochloride and chondroitin sulfate vs celecoxib for painful knee osteoarthritis. Basic and Clinical Pharmacology and Toxicology. 2014 September;115 SUPPL. 2:25.

18. Jain A, Patel S, Aggarwal S, et al. Autologous platelet derived growth factors as a treatment modality in early osteoarthritis knee-a prospective randomized control trial. Vox Sanguinis. 2012 July;103 SUPPL. 1:61.

19. Knoop J, Dekker J, Dan Der Leeden M, et al. Knee joint stabilization therapy in patients with osteoarthritis of the knee: A randomized, controlled trial. Arthritis and rheumatism; 2012. p. S116.

20. Lee B, Cho J, Kim T, et al. Tissuegene-C (TG-C) improved clinical scores in patients with osteoarthritis: A phase 2b study. Osteoarthritis and Cartilage. 2014 April;22 SUPPL. 1:S194.

21. Matias A, Trombini-Souza F, Yokota M, et al. Long-term effect of a flexible minimalist shoe on algofunctional, analgesic medication intake and gait kinematic in elderly women with knee osteoarthritis. Osteoarthritis and cartilage; 2014. p. S198.

22. Micca JL, Risser RC, Ahl J, et al. The efficacy and safety of duloxetine treatment in older patients with osteoarthritis knee pain: A post hoc, subgroup analysis of data from 2 placebo-controlled trials. Arthritis and Rheumatism. 2011;63(10):2011-11.

23. Nelson F, Zvirbulis R, Pilla AA. Non-invasive electromagnetic field therapy produces rapid and substantial pain reduction in early knee osteoarthritis: A randomized double-blind pilot study. Osteoarthritis and Cartilage. 2012 April;20 SUPPL. 1:S174.

24. Peniston JH, Gold MS, Alwine LK. An open-label, long-term safety and tolerability trial of diclofenac sodium 1% gel in patients with knee osteoarthritis. Phys Sportsmed. 2011 Sep;39(3):31-8. doi: 10.3810/psm.2011.09.1918. PMID: 22030938.

25. Provenza JR, Shinjo SK, Silva JM, et al. Combined glucosamine and chondroitin sulfate, once or three times daily, provides clinically relevant analgesia in knee osteoarthritis. Clin Rheumatol. 2015 Aug;34(8):1455-62. doi: 10.1007/s10067-014-2757-1. PMID: 25085275.

26. Rabago DP, Miller DJ, Zgierska AE, et al. Dextrose prolotherapy for knee osteoarthritis: Results of a randomized controlled trial. Osteoarthritis and cartilage; 2011. p. S142-s3.

27. Raynauld JP, Martel-Pelletier J, Dorais M, et al. Prediction of total knee replacement in a 6-month multicentre clinical trila with chondroitin sulfate in knee osteoarthritis: Results from a 4-year observation. Osteoarthritis and Cartilage. 2012 April;20 SUPPL. 1:S175.

28. Reginster J, Tajana E. Single oral dose of (1200 MG) sachet of chondroitin 4&6 sulfate (CS4&6-chondrosulf(registered trademark)) relieves pain and improves function. Results of a double blind study, versus placebo and an active treatment in knee OA patients. Osteoarthritis and Cartilage. 2011 September;19 SUPPL. 1:S226-S7.

29. Sattari S, Ashraf A. Comparison of the effects of 3-point valgus knee support and lateral wedge insoles in medial compartment knee osteoarthritis. Iranian Red Crescent Medical Journal. 2011 2011;13(9):581-4. PMID: 2011508100.

30. Segal N, Glass N, Teran-Yengle P, et al. Intensive Gait Training for Older Adults with Symptomatic Knee Osteoarthritis. American journal of physical medicine & rehabilitation / Association of Academic Physiatrists; 2015. p. 848-58.

31. Snyder-Mackler L. Lateral wedge insoles worn for 12 months provided no symptomatic or structural benefit for people with medial knee osteoarthritis. Journal of Physiotherapy. 2011 September;57(3):195.

32. Sung-Bum JU, Gi Duck P, Sang-Soo KIM. Effects of proprioceptive circuit exercise on knee joint pain and muscle function in patients with knee osteoarthritis. Journal of Physical Therapy Science. 2015;27(8):2439-41. PMID: 109081584. Language: English. Entry Date: 20151013. Revision Date: 20151013. Publication Type: Article.

33. Teixeira PE, Piva SR, Fitzgerald GK. Effects of impairment-based exercise on performance of specific self-reported functional tasks in individuals with knee osteoarthritis. Phys Ther. 2011 Dec;91(12):1752-65. doi: 10.2522/ptj.20100269. PMID: 22003157.

34. Tsai PF, Chang JY, Beck C, et al. A supplemental report to a randomized cluster trial of a 20-week Sun-style Tai Chi for osteoarthritic knee pain in elders with cognitive impairment. Complementary Therapies in Medicine. 2015 Aug;23(4):570-6. PMID: WOS:000360419700007.

35. Vincent KR, Montero C, Vincent HK. Progressive enhanced eccentric or concentric resistance exercise training for knee osteoarthritis. Osteoarthritis and cartilage; 2013. p. S275-s6.

36. Wang C, Schmid C, Iversen MD, et al. Comparative Effectiveness of Tai Chi Versus Physical Therapy in Treating Knee Osteoarthritis: A Randomized, Single-Blind Trial [abstract]. Arthritis Rheumatol. 2015;67(suppl 10).

37. Wang C, Schmid CH, Iversen MD, et al. Comparative Effectiveness of Tai Chi Versus Physical Therapy for Knee Osteoarthritis: A Randomized Trial. Ann Intern Med. 2016 Jul 19;165(2):77-86. doi: 10.7326/m15-2143. PMID: 27183035.

38. Wang P, Yang L, Li H, et al. Effects of whole-body vibration training with quadriceps strengthening exercise on functioning and gait parameters in patients with medial compartment knee osteoarthritis: A randomised controlled preliminary study. Physiotherapy (United Kingdom); 2016. p. 86-92.

39. Yildiz S, Özkan F, Akta I, et al. The effectiveness of ultrasound treatment for the management of knee osteoarthritis: a randomized, placebo-controlled, double-blind study. Turkish journal of medical sciences; 2015. p. 1187-91.

Appendix C. Evidence Table for All Included Studies

Table C1. Evidence table for all included studies

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Abbott, 2015[65] Study design: RCT Trial name: None Study Location: New Zealand Health care setting: Academic orthopedic surgery clinic/department, Physical therapy outpatient clinic Single Site	Total n = 75 Mean Age: 64 Arm 1, Mean Age: 64(10) BMI: 29.2(6.1) Arm 2, Mean Age: 65(10) BMI: 30.2(5.6) Arm 3, Mean Age: 61(12) BMI: 27.6(4.7) Arm 4, Mean Age: 64(10.2) BMI: 29.8(6.6) Female: 62% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Subtype: NR Diagnosis: ACR Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: 40 ACR: NA	Surgery knee limb in prior previous hip or knee replacement of the affected joint or any other surgical procedure in the previous 6 months month(s) Pending surgery Analgesics use in the previous Injected opioid or analgesic use in the previous 30 days month(s) Injected corticosteroids in the prior 30 days, hip or knee month(s) RA Physical impairments that would prevent participation Inability to comprehend study instructions or to attend and complete the sessions and follow-up	Arm 1: Land-based exercise n = 19 Placebo/ Dose: 45 minutes per session Frequency: 12 sessions per 9 weeks Duration: 9 weeks Method of Blinding: NA Co-Intervention: none Arm 2: Land-based exercise n = 19 Dose: 45 minutes per session Frequency: 8 sessions in 9 weeks, 2 booster sessions at 5 months, 1 session at 8 months, 1 session at 11 months Duration: 11 months Method of Blinding: NA Co-Intervention: Booster sessions at 5, 8, and 11 months Arm 3: Land-based exercise + manipulation n = 18 Dose: 45 minutes per exercise session and 30-45 minutes per manual therapy session Frequency: 12 sessions exercise and manual therapy each in 9 weeks Duration: 9 weeks Method of Blinding: NA Co-Intervention: Manual therapy Arm 4: Land-based exercise plus manipulation n = 19 Dose: 45 minutes per exercise session and 30-45 minutes per manual therapy session Frequency: 12 sessions exercise and manual therapy each in 9 weeks plus 2 booster sessions at 5 months, 1 session at 8 months, 1 session at 11 months Duration: 11 months Method of Blinding: NA Co-Intervention: Booster sessions plus manual therapy	<u>TUG (s):</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -1.00 95% CI: (-2.58, 0.58) Comparator: Arm 3 vs Arm 1 , MD : 0.00 95% CI: (-1.42, 1.42) Comparator: Arm 4 vs Arm 1 , MD : -0.10 95% CI: (-2.02, 1.82) <u>WOMAC total:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -56.10 95% CI: (-92.70, -19.50) Comparator: Arm 3 vs Arm 1 , MD : -39.20 95% CI: (-69.38, -9.02) Comparator: Arm 4 vs Arm 1 , MD : -8.30 95% CI: (-41.90, 25.30) <u>Pain intensity score:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -2.00 95% CI: (-3.84, -0.16) Comparator: Arm 3 vs Arm 1 , MD : -2.30 95% CI: (-4.07, -0.53) Comparator: Arm 4 vs Arm 1 , MD : 0.20 95% CI: (-1.86, 2.26)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Acosta-Olivo, 2014[26] Study design: RCT Trial name: None Study Location: Mexico Health care setting: Academic orthopedic surgery clinic/department Single Site	Total n = 42 Age Range: NR Arm 1, Mean Age: NR BMI: NR Arm 2, Mean Age: NR BMI: NR Female: NR Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: K-L: Grade I Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: 3 months Minimum Age: 40 Able to sign Consent Without previous treatment NR	Surgery knee limb in prior 2 months month(s) Prior experience with the intervention of interest Use of anticoagulants Varus-valgus deformities Prior arthritis in the knee Autoimmune disorders Cerebrovascular diseases; hemoglobin <11; drug or alcohol abuse; active infections	Arm 1: Control n = 21 Dose: 1g paracetamol Frequency: 3 times per day Duration: 1 month Arm 2: Cell-based therapies n = 21 Dose: 5 ml plasma per injection Frequency: 2 doses per month Duration: 1 month	<u>KOOS:</u> Follow-Up Time: 4 months : Comparator: Arm 2 vs Arm 1 , MD : -9.00 95% CI: (-18.11, 0.11) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -6.90 95% CI: (-18.29, 4.49)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Atamaz, 2012[87] Study design: RCT Trial name: None Study Location: NR Health care setting: NR Multiple Sites: 4	Total n = 203 Total # of knees = NR Age Range: NR Arm 1, Mean Age: 60.7 (SD 6.5) BMI: 29.0 (SD 4.1) Arm 2, Mean Age: 61.9 (SD 6.9) BMI: 28.4 (SD 3.5) Female: 82.3% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: 2&3, ~Symptomatic with at least 40mm or 4cm severity of pain on the VAS for at least 6 months, ACR Analgesic Use: Yes, Patients were asked to discontinue any pretreatment with NSAIDs drugs 7 days before the start of the study. If the patient required analgesic medication for knee pain, paracetamol use was permitted and noted.	Diagnosis of osteoarthritis of the knee Duration of Symptoms: 6 months Minimum Age: 51 Maximum Age:79 Otherwise Healthy K-L: 2&3 ACR: confirmed knee OA	Concomitant medical problems that prevent participation Surgery knee limb in prior 6 month(s) Injected hyaluronic acid in the past or during the past 6 month(s) Injected corticosteroids in the prior 1 month(s) Prior experience with the intervention of interest Diagnosis of joint infection, a specific condition (neoplasm, diabetes mellitus, paresis, osteonecrosis, recent trauma, etc.), ascertained/suspected pregnancy or lactation, and poor general health status that would interfere with the functional assessments History of any contraindication for electrotherapy Received corticosteroid therapy or chondroprotective agents during the 30 days prior to the study or viscosupplementation treatment within 6 months prior to the study Undergone previous major surgery, such as joint replacement or arthroscopy, within 6 months prior to the study	Arm 1: Sham n = 37, Placebo/Sham TENS, Dose: 20 minutes, Frequency: 5 times per week, Duration: 3 weeks Method of Blinding: All patients, investigators, and analysts were blinded, with the exception of members of the data and safety monitoring board Co-Intervention: Exercise program in groups of 4-5 patients led by a physiotherapist 3x/week for 3 weeks, included 5- to 6-minutes of jogging, stretching exercises (approx. 10min), isometric quadriceps exercises (10–15 repetitions) in the seated position were performed for 10 seconds with 10-second breaks, and chair lift and mini squats exercises (10–15 reps). At the end of 3 weeks, the physiotherapist prescribed a home-based training program (3x/week) as well as group exercise. Before the treatments, all patients participated in a single education group session of approximately 1-hour duration. Arm 2: Neuromuscular electrical stimulation n = 37, Dose: 80Hz with 10- to 30-mA intensity for 20 minutes, Frequency: 5 times per week, Duration: 3 weeks Method of Blinding: All patients, investigators, and analysts were blinded, with the exception of members of the data and safety monitoring board Co-Intervention: Exercise program in groups of 4-5 patients led by a physiotherapist 3x/week for 3 weeks, included 5- to 6-minutes of jogging, stretching exercises (approx. 10min), isometric quadriceps exercises (10–15 repetitions) in the seated position were performed for 10 seconds with 10-second breaks, and chair lift and mini squats exercises (10–15 reps).	<u>VAS pain:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : 4.30 95% CI: (-5.99, 14.59) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : 0.20 95% CI: (-11.23, 11.63) <u>WOMAC function:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : -2.50 95% CI: (-8.66, 3.66) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -2.50 95% CI: (-9.73, 4.73) <u>WOMAC pain:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : -1.40 95% CI: (-3.69, 0.89) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -1.30 95% CI: (-3.89, 1.29)
Atamaz, 2012[87] - Continued				At the end of 3 weeks, the physiotherapist prescribed a home-based training program (3x/week) as well as group exercise. Before the treatments, all patients participated in a single education group session of approximately 1-hour duration. Arm 3-6 : Not of Interest	

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Atkins, 2013[122] Study design: RCT Trial name: None Study Location: US Health care setting: Wellness center Single Site	Total n = 40 Total # of knees = NR Age Range: NR Arm 1, Mean Age: NR BMI: NR Arm 2, Mean Age: NR BMI: NR Female: NR Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: Written diagnosis of knee OA by participants' health care provider Analgesic Use: NR	Minimum Age: 50 Ambulatory Willingness to attend 75% of scheduled self-massage sessions No limitations that prevented mobility of the knee Knee pain, pain on most days of the prior month, and morning stiffness lasting less than 30 minutes Crepitus on motion and bony enlargement at affected joints Agreement to practice no new exercise or stretching program and commitment to receiving no other mas sage therapy during the study	Concomitant medical problems that prevent participation Prior surgery on one or both knees Surgery knee limb in prior 6 month(s) Injected corticosteroids in the prior 3 month(s) Active rheumatoid arthritis or other serious medical conditions Intra-articular knee injection of a steroid within the previous 3 months Surgical procedure on either lower extremity within the past 6 months	Arm 1: Control n = 19 Placebo/Control, wait list Dose: NA Frequency: NA Duration: 12 weeks Method of Blinding: None Co-Intervention: Usual care only and received optional future dates for the knee self-massage training Arm 2: Massage n = 21 Dose: Supervised sessions were 1 hour, including 20 minutes of the intervention. During the unsupervised weeks, participants were encouraged to continue their twice-weekly practice of self-massage. Frequency: 2 times per week Duration: 12 weeks Method of Blinding: None Co-Intervention: Usual care	<u>WOMAC function:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.80 95% CI: (NC, NC) <u>WOMAC pain:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.65 95% CI: (NC, NC) <u>WOMAC total:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.70 95% CI: (NC, NC)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Atukorala, 2016[128] Study design: Single arm trial Trial name: Healthy weight for life Study Location: Australia Health care setting: internet and phone-based program Multiple Sites: NR (internet-based)	Total n = 1383 Mean Age(SD): Mean age 64.0(8.7) Arm 1, Mean Age: 64(8.7) BMI: 34.4(5.2) Female: 70.9% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: K-L: not specified, Mean KOOS pain 56.3(6.8) Analgesic Use: NR	Diagnosis of osteoarthritis of the knee BMI>28 Referral to orthopedist for KR Enrollment in OAHWFL program Radiographic or arthroscopy: NR	Exclusion : NR	Arm 1: Weight loss and exercise n = 1383 Dose: NA Frequency: NA Duration: 18 weeks	<u>KOOS function:</u> Follow-Up Time: 18 weeks : Comparator: >10% weight change (post-pre) , MD : 17.40 95% CI: (15.9, 18.9) Comparator: 7.6-10% weight change (post-pre) , MD : 13.60 95% CI: (11.9, 15.3) Comparator: 5.1-7.5% weight change (post-pre) , MD : 12.00 95% CI: (10.2, 13.8) Comparator: 2.5-5% weight change (post-pre) , MD : 8.90 95% CI: (7.0, 10.8) Comparator: <2.5% weight change (post-pre) , MD : 7.80 95% CI: (4.8, 10.8) <u>KOOS pain:</u> Follow-Up Time: 18 weeks : Comparator: >10% weight change (post-pre) , MD : 16.70 95% CI: (15.2, 18.2) Comparator: 7.6-10% weight change (post-pre) , MD : 13.30 95% CI: (11.6, 15.0) Comparator: 5.1-7.5% weight change (post-pre) , MD : 12.00 95% CI: (10.2, 13.8) Comparator: 2.5-5% weight change (post-pre) , MD : 9.90 95% CI: (7.7, 12.1) Comparator: <2.5% weight change (post-pre) , MD : 6.10 95% CI: (3.2, 9.0)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Avelar, 2011[93] Study design: RCT Trial name: None Study Location: NR Health care setting: NR Site size: NR	Total n = 23 Total # of knees = NR Age Range: NR Arm 1, Mean Age: 71 (SD 4) BMI: NR Arm 2, Mean Age: 75 (SD 5) BMI: NR Female: 86.96% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: bilateral 34.8% (of 21), unilateral 56.5% (of 21) Subtype: NR Diagnosis: K-L: 1-4, Knee OA in at least 1 knee clinical and radiographic criteria according to ACR Analgesic Use: NR	Minimum Age: 60 Ambulatory Able to sign Consent Not requiring a walking aid Any cognitive deficit as determined by the Mini-Mental Status Examination	Concomitant medical problems that prevent participation Concomitant or prior use of other meds Prior acute injury to the knee Not having suffered any recent knee injury Any orthopedic, neurological, respiratory, or acute cardiac diseases that would preclude the study Not having been submitted to any rehabilitation procedure in the previous 3 months Not having used glucocorticoids for at least 2 months prior the study	Arm 1: Control n = 11 Placebo/Control Dose: NA Frequency: NA Duration: 12 weeks Method of Blinding: Blinded, not otherwise described Co-Intervention: Squatting exercises, for each repetition, individuals were instructed to perform 3 seconds of isometric flexion of the quadriceps to 60 degrees and 3 seconds of isometric flexion of the quadriceps to 10 degrees. Prior to the squatting exercises, both groups warmed-up on an ergometric bicycle at 70% of the predicted maximum heart rate for age for 10 minutes Arm 2: Vibrating platform (whole body vibration) n = 12 Dose: Frequency of 35Hz–40Hz, amplitude of 4mm, and acceleration that ranged from 2.78G to 3.26G Frequency: 3 times per week Duration: 12 weeks Method of Blinding: Blinded, not otherwise described Co-Intervention: Squatting exercises, for each repetition, individuals were instructed to perform 3 seconds of isometric flexion of the quadriceps to 60 degrees and 3 seconds of isometric flexion of the quadriceps to 10 degrees. Prior to the squatting exercises, both groups warmed-up on an ergometric bicycle at 70% of the predicted maximum heart rate for age for 10 minutes	<u>6 min walk (meter):</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -27.62 95% CI: (-76.92, 21.68) <u>TGUG (s):</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.02 95% CI: (-0.93, 0.97) <u>WOMAC function:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -59.00 95% CI: (-373.43, 255.43) <u>WOMAC pain:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : 24.00 95% CI: (-60.64, 108.64)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Azlin, 2011[116] Study design: RCT Trial name: None Study Location: Malaysia Health care setting: Physiotherapy unit in academic medical center Single Site	Total n = 13 Age Range: 40 Arm 1, Mean Age: 59.7(4.9) BMI: 26.2 Arm 2, Mean Age: 63.1 (10.8) BMI: 28.5 Female: 85% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: bilateral 85%, unilateral 15% Subtype: NR Diagnosis: By orthopedic specialist Analgesic Use: Yes, Continued normal medications	Diagnosis of osteoarthritis of the knee: By orthopedic specialist Ambulatory Ascend and descend at least a flight of stair Willingness to be randomized Sub-acute or chronic OA Number of knees >=1	Concomitant medical problems that prevent participation Prior surgery on one or both knees Prior acute injury to the knee Acute inflammation or contracture Cognitive problem (MMSE<20) Pain during exercise	Arm 1: Control n = 6 Placebo/Conventional physical therapy Frequency: Twice a week Duration: 4 weeks Arm 2: Passive joint mobilization n = 7 Frequency: Twice a week Duration: 4 weeks Co-Intervention: Conventional physiotherapy (exercises followed by thermal therapy with hot pack)	<u>VAS pain stairs:</u> Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.99 95% CI: (-21.54, 15.56)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Bagnato, 2016[92] Study design: RCT Trial name: None Study Location: Italy Health care setting: Academic rheumatology clinic/department Single Site	Total n = 66 Age Range: >=40 Arm 1, Mean Age: 66.9 (10) BMI: 27.1 (4.1) Arm 2, Mean Age: 68.6 (11.9) BMI: 27.7 (4.6) Female: 72% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: A diagnosis of primary OA of the knee according to the ACR criteria, including radiological evidence of OA Analgesic Use: Yes, 43% of total used analgesics; 40% of tx group and 46% of control group	Diagnosis of osteoarthritis of the knee Duration of Symptoms: >=6 months Minimum Age: >=40 Persistent pain despite receiving the maximal tolerated doses of conventional medical therapy, including acetaminophen and/or an NSAID, with persistent pain defined as a minimal mean score of 40 mm on the VAS for global pain Daily pain during the month prior to study enrolment Ability to attend follow-up appointments No change in pain medication during the last month ACR: a diagnosis of primary OA of the knee according to the ACR criteria, including radiological evidence of OA	Concomitant medical problems that prevent participation Concomitant or prior use of other meds Injected corticosteroids in the prior month(s) Patients affected by secondary causes of OA, DIP joint OA, local or systemic infection, secondary FM, diabetes mellitus, systemic arthritis, coagulopathy, patients on anticoagulant therapy and patients who had received previous intra-articular steroid injection or with avascular necrosis of bone were excluded.	Arm 1: Sham PEMF n = 33 Placebo/Sham Dose: 12 hours Frequency: Daily Duration: 4 weeks Method of Blinding: Double blind Arm 2: Pulsed electromagnetic fields (PEMF) n = 33 Dose: 12 hours Frequency: Daily Duration: 4 weeks Method of Blinding: Double bind	<u>SF-36 mental health:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : -0.20 95% CI: (-2.32, 1.92) <u>SF-36 physical health:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : -2.70 95% CI: (-5.81, 0.41) <u>VAS pain:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : -11.30 95% CI: (-19.17, -3.43) <u>WOMAC function:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : -8.00 95% CI: (-26.32, 10.32) <u>WOMAC pain:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : -5.20 95% CI: (-9.72, -0.68) <u>WOMAC total:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : -14.70 95% CI: (-36.83, 7.43)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Barduzzi, 2013[59] Study design: RCT Trial name: None Study Location: Brazil Health care setting: NR Site size: NR	Total n = 15 Arm 1, Mean Age: 70.8(6.3) BMI: NR Arm 2, Mean Age: 71.6(7.0) BMI: NR Arm 3, Mean Age: 66.4(5.1) BMI: NR Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: bilateral 60% Subtype: NR Diagnosis: ACR Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: 60 Maximum Age:79 Able to sign Consent ACR: NA	Concomitant medical problems that prevent participation Pending surgery Physical Therapy or Rehab or exercise in the previous 3 months month(s) Use of assistive walking devices Neurological dysfunction that promoted cognitive changes	Arm 1: Control n = 5 Dose: NA Frequency: NA Duration: NA Arm 2: Water based physical therapy n = 5 Dose: 60 minutes per session (2-4 sets, 20-25 repetitions) Frequency: 3 sessions per week Duration: 4 months (45 day break between 12th and 13th session) 24 sessions total Arm 3: Land-based physical therapy n = 5 Dose: 60 minutes per session (2-4 sets, 20-25 repetitions) Frequency: 3 sessions per week Duration: 4 months (45 day break between 12th and 13th session) 24 sessions total	<u>Walking speed:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : -1.18 95% CI: (-5.39, 3.03) Comparator: Arm 3 vs Arm 1 , MD : -0.29 95% CI: (-4.77, 4.19) Follow-Up Time: 4.5 months : Comparator: Arm 3 vs Arm 2 , MD : 4.03 95% CI: (-0.51, 8.57)
Bartels, 2014[68] Study design: Single arm trial Trial name: CAROT Study Location: Denmark Health care setting: NR Site size: NR	Total n = 192 Total # of knees = NR Mean Age(SD): 62.6 (SD 6.3) (for 175 who Arm 1, Mean Age: 62.6 (SD 6.3) BMI: 37.1 (SD 4.4) Female: NR Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: ACR primary knee OA Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: 51 BMI >= 30 kg/m 2 ACR: Primary knee OA NR: Clinical symptoms and radiographic verification of the diagnosis	Exclusion : NR	Arm 1: Weight loss, self-management n = 192 Dose: 8-week formula weight loss diet 415-810 kcal/day, followed by 8 weeks on a hypo-energetic 1200 kcal/day diet of normal food and formula products Frequency: Diet was daily. Weekly sessions (1.5 h/week) by a dietician giving nutritional instructions and behavioral therapy Duration: 16 weeks Method of Blinding: NA Co-Intervention: NR	<u>KOOS function:</u> Follow-Up Time: 16 weeks : Comparator: post-pre , MD : 12.10 95% CI: (10.0, 14.2) <u>KOOS pain:</u> Follow-Up Time: 16 weeks : Comparator: post-pre , MD : 10.70 95% CI: (8.5, 12.9) <u>Weight (kg):</u> Follow-Up Time: 16 weeks : Comparator: pre-post , MD : 14.00 95% CI: (13.3, 14.7)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Bellare, 2014[30] Study design: RCT Trial name: None Study Location: India Health care setting: Orthopedic clinics Multiple Sites: 3	Total n = 117 Age Range: >=50 Arm 1, Mean Age: 60.70 (8.31) BMI: 27.68 (3.03) Arm 2, Mean Age: 59.98 (8.81) BMI: 27.36 (3.71) Female: 23% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: ACR Analgesic Use: Yes	Diagnosis of osteoarthritis of the knee: ACR	Exclusion : NR	Arm 1: Diet therapy n = 56 Dose: 1200-1400 kcal/d Duration: 1 year Arm 2: Diet therapy + Glucosamine-chondroitin n = 61 Dose: Glucosamine 1500mg/day; Chondroitin 1200mg/day Frequency: Twice daily (G 750mg+C 600mg) Duration: 1 year	<u>Lequesne Index Score:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -3.20 95% CI: (-3.86, -2.54) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -2.56 95% CI: (-3.35, -1.77) <u>VAS score:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -1.70 95% CI: (-1.99, -1.41) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -2.08 95% CI: (-2.40, -1.76) <u>WOMAC function:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -7.90 95% CI: (-10.06, -5.74) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -3.86 95% CI: (-6.16, -1.56) <u>WOMAC pain:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -3.10 95% CI: (-3.69, -2.51) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -1.59 95% CI: (-2.31, -0.87)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Bennell, 2011[109] Study design: RCT Trial name: None Study Location: Australia Health care setting: NR Site size: NR	Total n = 200 Age Range: >=50 Arm 1, Mean Age: 65.0 (7.9) BMI: 30.4 (5.6) Arm 2, Mean Age: 63.3 (8.1) BMI: 28.1 (4.2) Female: 58% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: Medial 100% Diagnosis: Radiological evidence Analgesic Use: Yes, Not specified	Diagnosis of osteoarthritis of the knee Minimum Age: 50 Able to sign Consent Pain on walking>=3 Radiological knee alignment <=185 degrees X-ray: Osteophytes or joint space narrowing in medial compartment	Concomitant medical problems that prevent participation Prior surgery on one or both knees Surgery knee limb in prior 6 month(s) Concomitant or prior use of other meds Injected corticosteroids in the prior 6 month(s) Prior experience with the intervention of interest K-L: 1 or 4 Predominant patellofemoral joint symptoms Systemic arthritic conditions	Arm 1: Control Insoles n = 97 Placebo/No-wedging insoles Frequency: All day every day Duration: 12 months Arm 2: Wedge Insoles n = 103 Frequency: All day every day Duration: 12 months	<u>Pain numerical rating scale:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : 0.00 95% CI: (-0.65, 0.65) <u>Quality of life:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : 0.00 95% CI: (-0.06, 0.06) <u>WOMAC function:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : 0.70 95% CI: (-2.79, 4.19) <u>WOMAC pain:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : 0.20 95% CI: (-0.75, 1.15)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Bennell, 2015[53] Study design: RCT Trial name: None Study Location: Australia Health care setting: Academic sports medicine clinic/department Single Site	Total n = 222 Mean Age: 63 Arm 1, Mean Age: 62.7 (7.9) BMI: 31.5 (5.9) Arm 2, Mean Age: 63.0 (7.9) BMI: 30.8 (6.4) Arm 3, Mean Age: 64.6 (8.3) BMI: 31.0 (6.0) Female: 60% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: bilateral 73%, unilateral 27% Diagnosis: K-L: 30% Grade II; 21% grade III; 23% grade IV Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: knee pain >=3 months Minimum Age: 50 Average pain >=40/100mm on VAS in preceding week At least moderate difficulty with daily functioning (WOMAC physical function _ 25/68 units) ACR Criteria: NA	Concomitant medical problems that prevent participation Surgery knee limb in prior 6 months month(s) Pending surgery Injected corticosteroids in the prior 3 months month(s) Physical Therapy or Rehab or exercise in the previous 6 months month(s) Prior experience with the intervention of interest Systemic arthritis Self-reported history of serious mental illness, such as schizophrenia, or self reported diagnosis of current clinical depression; neurological condition such as Parkinson's disease, multiple sclerosis or stroke Walking exercise for >30 minutes continuously daily; participating in a regular (more than twice a week) structured and/or supervised exercise program such as attending exercise classes in a gym or use of a personal trainer	Arm 1: Land-based Exercise strength/resistance training n = 75 Dose: 25 minutes exercise Frequency: 10 sessions per 12 weeks plus home practice Duration: 12 weeks Arm 2: Self-management n = 74 Dose: NR Frequency: 10 sessions per 12 weeks plus home practice Duration: 12 weeks Arm 3: Self-management plus Land-based exercise: strength training n = 73 Dose: 25 minute exercise sessions plus educational session Frequency: 10 sessions per 12 weeks plus home practice Duration: 12 weeks	<u>AQoL-6D:</u> Follow-Up Time: 12 weeks : Comparator: Arm 3 vs Arm 2 , MD : -0.02 95% CI: (-0.07, 0.03) Follow-Up Time: 52 weeks : Comparator: Arm 3 vs Arm 2 , MD : -0.03 95% CI: (-0.07, 0.01) <u>TUG (s):</u> Follow-Up Time: 12 weeks : Comparator: Arm 3 vs Arm 2 , MD : -1.10 95% CI: (-1.97, -0.23) Follow-Up Time: 52 weeks : Comparator: Arm 3 vs Arm 2 , MD : -1.10 95% CI: (-1.84, -0.36) <u>VAS overall pain:</u> Follow-Up Time: 12 weeks : Comparator: Arm 3 vs Arm 2 , MD : -6.80 95% CI: (-13.73, 0.13) Follow-Up Time: 52 weeks : Comparator: Arm 3 vs Arm 2 , MD : -3.10 95% CI: (-10.78, 4.58) <u>VAS walking:</u> Follow-Up Time: 12 weeks : Comparator: Arm 3 vs Arm 2 , MD : -8.20 95% CI: (-15.41, -0.99) Follow-Up Time: 52 weeks : Comparator: Arm 3 vs Arm 2 , MD : -4.90 95% CI: (-13.21, 3.41)
Bennell, 2015[53] - Continued			Inability to walk unaided Inadequate written and spoken English; inability to comply with the study protocol such as inability to attend physical therapy sessions or attend assessment appointments at the University		<u>WOMAC function:</u> Follow-Up Time: 12 weeks : Comparator: Arm 3 vs Arm 2 , MD : -8.10 95% CI: (-11.46, -4.74) Follow-Up Time: 52 weeks : Comparator: Arm 3 vs Arm 2 , MD : -5.30 95% CI: (-8.82, -1.78) <u>WOMAC pain:</u> Follow-Up Time: 12 weeks : Comparator: Arm 3 vs Arm 2 , MD : -1.50 95% CI: (-2.50, -0.50) Follow-Up Time: 52 weeks : Comparator: Arm 3 vs Arm 2 , MD : -0.60 95% CI: (-1.70, 0.50)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Bliddal, 2011[126] Study design: RCT Trial name: None Study Location: Denmark Health care setting: Home, NR Site size: NR	Total n = 96 Age Range: 36-90 Arm 1, Mean Age: 64.1 (10.5) BMI: 35.2 (4.5) Arm 2, Mean Age: 61.1 (11.1) BMI: 35 (5.5) Female: 89% Racial/Ethnic Distribution: NR Living Situation: NR Subtype: NR Diagnosis: K-L: 2&3, ACR Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: 18 Overweight was defined as a body mass index (BMI) _28 kg/m2. Only patients who explicitly expressed a clear, unequivocal desire for weight loss Fluent in Danish ACR	Concomitant medical problems that prevent participation History of other rheumatic diseases possibly responsible for secondary OA, diabetes mellitus or other endocrine disorders, and substantial abnormalities in haematological, hepatic, renal or cardiac function	Arm 1: Conventional diet program n = 45 Placebo/Control Dose: 1200 calories/day Frequency: Daily Duration: 52 weeks Method of Blinding: Single-blinded Arm 2: Low-energy diet n = 44 Dose: 810-1200 cal/day Frequency: Daily Duration: 52 weeks Method of Blinding: Single-blinded	<u>WOMAC disability:</u> Follow-Up Time: 52 weeks : Comparator: Arm 2 vs Arm 1 , MD : -3.60 95% CI: (-9.14, 1.94) <u>WOMAC pain:</u> Follow-Up Time: 52 weeks : Comparator: Arm 2 vs Arm 1 , MD : -7.20 95% CI: (-13.30, -1.10) <u>WOMAC total:</u> Follow-Up Time: 52 weeks : Comparator: Arm 2 vs Arm 1 , MD : -4.30 95% CI: (-9.57, 0.97) <u>Weightloss, kg:</u> Follow-Up Time: 52 weeks : Comparator: Arm 2 vs Arm 1 , MD : -7.30 95% CI: (-9.52, -5.08)
Bokaeian, 2016[99] Study design: RCT Trial name: None Study Location: Iran Health care setting: NR Site size: NR	Total n = 28 Age Range: 35-76 Arm 1, Mean Age: 54.0 (3.9) Arm 2, Mean Age: 51.8 (8.3) Female: 93% Racial/Ethnic Distribution: NR Living Situation: NR Subtype: Tibiofemoral 100% Diagnosis: K-L: mild to moderate chronic osteoarthritis of unilaterally or bilaterally tibiofe moral joint according to the method of Kellgren & Lawrence Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: >1 month Minimum Age: >35 Maximum Age:76 Ambulatory K-L: mild to moderate	Concomitant medical problems that prevent participation Surgery knee limb in prior 3 months month(s) Injected hyaluronic acid in the past or during the past 3 months month(s) Injected corticosteroids in the prior 3 months month(s) Other dis eases such as: diabetes, diseases of musculoskeletal, neuromuscular, cardiovascular, respiratory, Having an artificial hip or knee joints, Medication History of trauma to knee joint during last week Performing regular professional exercise and extreme physical weakness	Arm 1: Strength training alone n = 13 Placebo/Strength training alone Dose: approx.11 min Frequency: 3 times a week Duration: 8 weeks Method of Blinding: Single-blind Arm 2: Whole body vibration + strength training n = 15 Dose: 30-70s, 6-9 sets Frequency: 3 times a week Duration: 8 weeks Method of Blinding: Single-blind Co-Intervention: Strength training	<u>VAS pain:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : 1.50 95% CI: (-0.80, 3.80) <u>WOMAC quality of life:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.80 95% CI: (-3.29, 4.89)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Brosseau, 2012[39] Study design: RCT Trial name: None Health care setting: Physical therapy outpatient clinic Single Site	Total n = 222 Mean Age(SD): Mean age 63.4(8.6) Arm 1, Mean Age: 62.3(6.8) BMI: 29.9(5.3) Arm 2, Mean Age: 63.9(10.3) BMI: 29.4(5.4) Female: 69% Racial/Ethnic Distribution: African American 2.3%, Asian 4.5%, Caucasian 88.7%, Hispanic 3.6%, 0.5% American Indian, 0.5% Other Living Situation: Community Dwelling Location of OA: bilateral 23%, unilateral 77% Subtype: NR Diagnosis: Mild to moderate according to ACR clinical and radiographic criteria Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: pain for at least 3 months Ambulatory Expected medications to change during study period Demonstrated ability to walk for a minimum of 20 minutes with minimal pain (<=3/10 on VAS) Able to be treated as outpatients Available 3 times a week for 12 months mild to moderate according to ACR clinical and radiographic criteria: NR	Injected hyaluronic acid in the past or during the past 12 months month(s) Injected corticosteroids in the prior 12 months month(s) Physical Therapy or Rehab or exercise in the previous regular activity program 2 or more times per week for more than 20 minutes per session during previous 6 months or rehab treatment within prior 12 months month(s) Severe OA of the knee or other weight bearing joints of the lower extremity Pain at rest or at night Any other treatment for knee OA besides analgesic for prior 12 months Uncontrolled HTN or other condition, such as rheumatoid arthritis that would make participation difficult Significant cognitive deficits, inability to communicate in English, intention to move within the year, unwillingness to sign consent	Arm 1: Control n = 74 Placebo/Educational materials (pamphlet) Dose: NA Frequency: NA Duration: 12 months Method of Blinding: NA Arm 2: Walking n = 79 Dose: 45 minutes walking and 20 minutes warm-up/cool down per session Frequency: 3 sessions per week Duration: 12 months Method of Blinding: NA Co-Intervention: Arm 3: Walking + Co-Intervention: behavioral intervention adapted from Program for Arthritis Control through Education and Exercise program: education and behavioral counseling	<u>6 min walk (meter):</u> Follow-Up Time: 18 months : Comparator: Arm 2 vs Arm 1 , MD : 47.44 95% CI: (4.45, 90.43) Comparator: Arm 3 vs Arm 1 , MD : 40.20 95% CI: (-1.29, 81.69) <u>SF-36 pain:</u> Follow-Up Time: 18 months : Comparator: Arm 2 vs Arm 1 , MD : 2.40 95% CI: (-5.89, 10.69) Comparator: Arm 3 vs Arm 1 , MD : 6.28 95% CI: (-1.94, 14.49) <u>SF-36 physical function:</u> Follow-Up Time: 18 months : Comparator: Arm 2 vs Arm 1 , MD : 7.54 95% CI: (-1.57, 16.64) Comparator: Arm 3 vs Arm 1 , MD : 12.44 95% CI: (2.30, 22.58) <u>TUG (s):</u> Follow-Up Time: 18 months : Comparator: Arm 2 vs Arm 1 , MD : 0.53 95% CI: (-0.35, 1.41) Comparator: Arm 3 vs Arm 1 , MD : 0.52 95% CI: (-0.23, 1.27) <u>WOMAC function:</u> Follow-Up Time: 18 months : Comparator: Arm 2 vs Arm 1 , MD : -1.20 95% CI: (-8.35, 5.95) Comparator: Arm 3 vs Arm 1 , MD : 4.75 95% CI: (-2.94, 12.44) <u>WOMAC pain:</u> Follow-Up Time: 18 months : Comparator: Arm 2 vs Arm 1 , MD : 0.10 95% CI: (-7.32, 7.52) Comparator: Arm 3 vs Arm 1 , MD : 2.66 95% CI: (-5.35, 10.67)
Brosseau, 2012[39] - Continued					<u>WOMAC total:</u> Follow-Up Time: 18 months : Comparator: Arm 2 vs Arm 1 , MD : -0.60 95% CI: (-7.54, 6.34) Comparator: Arm 3 vs Arm 1 , MD : 4.68 95% CI: (-2.80, 12.16)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Bruce-Brand, 2012[44] Study design: RCT Trial name: None Study Location: Ireland Health care setting: Academic orthopedic surgery clinic/department Single Site	Total n = 26 Mean Age: 64 Arm 1, Mean Age: 65.2 ± 3.1 BMI: 31.7 ± 4.1 Arm 2, Mean Age: 63.4 ± 5.9 BMI: 33.9 ± 8.3 Arm 3, Mean Age: 63.9 ± 5.8 BMI: 33.7 ± 5.6 Female: 42% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: K-L: 3&4, Moderate-to-severe, Outerbridge Scale 3-4 Analgesic Use: Yes, Subjects in all 3 groups were advised to maintain any pre-existing treatment of their OA such as pharmacologic therapy.	Diagnosis of osteoarthritis of the knee Minimum Age: 55 Maximum Age:74 Ambulatory Wait list for arthroplasty K-L: 3&4 Outerbridge scale: 3-4	Surgery knee limb in prior 3 month(s) Pending surgery Physical Therapy or Rehab or exercise in the previous 6 months month(s) Prior experience with the intervention of interest Medical co-morbidities precluding participation in an exercise program Implanted electrical devices Neurological disorders, inflammatory arthritis Significant cognitive impairment Anticoagulant therapy	Arm 1: Standard care n = 6 Placebo/OA education, weight loss, pharmacologic therapy, and physical therapy Dose: not applicable Frequency: not applicable Duration: 6 weeks Arm 2: Strength/resistance training n = 10 Dose: 30 minutes Frequency: 3 sessions per week Duration: 6 weeks Arm 3: NMES n = 10 Dose: 20 minutes per session Frequency: 5 sessions per week Duration: 6 weeks	<u>SF-36 mental:</u> Follow-Up Time: 14 weeks : Comparator: Arm 2 vs Arm 1 , MD : 5.20 95% CI: (-18.46, 28.86) Comparator: Arm 3 vs Arm 1 , MD : 5.10 95% CI: (-14.55, 24.75) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.64 95% CI: (-23.41, 20.13) Comparator: Arm 3 vs Arm 1 , MD : -5.67 95% CI: (-27.62, 16.28) <u>SF-36 physical:</u> Follow-Up Time: 14 weeks : Comparator: Arm 2 vs Arm 1 , MD : 14.63 95% CI: (-8.68, 37.94) Comparator: Arm 3 vs Arm 1 , MD : 20.23 95% CI: (1.63, 38.83) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : 6.00 95% CI: (-15.16, 27.16) Comparator: Arm 3 vs Arm 1 , MD : 5.50 95% CI: (-13.19, 24.19) <u>WOMAC function:</u> Follow-Up Time: 14 weeks : Comparator: Arm 2 vs Arm 1 , MD : 9.83 95% CI: (-7.73, 27.39) Comparator: Arm 3 vs Arm 1 , MD : 9.83 95% CI: (-7.20, 26.86) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : 7.80 95% CI: (-4.79, 20.39) Comparator: Arm 3 vs Arm 1 , MD : 7.77 95% CI: (-4.54, 20.08) <u>WOMAC pain:</u> Follow-Up Time: 14 weeks : Comparator: Arm 2 vs Arm 1 , MD : 1.27 95% CI: (-2.88, 5.42) Comparator: Arm 3 vs Arm 1 , MD : 0.17 95% CI: (-3.50, 3.84)
Bruce-Brand, 2012[44] -Continued					Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : 2.45 95% CI: (-1.37, 6.27) Comparator: Arm 3 vs Arm 1 , MD : 0.55 95% CI: (-2.85, 3.95)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Bruyere, 2008[33] Study design: Post-hoc analysis Trial name: None Study Location: Belgium, Czech Republic Health care setting: Academic orthopedic surgery clinic/department, Institute of Rheumatology Multiple Sites: 2	Total n = 275 Age Range: 63.2 Arm 1, Mean Age: 63.6 BMI: 26.6 Arm 2, Mean Age: 62.9 BMI: 26.6 Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: ACR Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Inclusion : NR ACR	Exclusion : NR	Arm 1: Placebo n = 131 Placebo/Tablets packets Dose: Frequency: Once daily Duration: 12 months Arm 2: Glucosamine sulfate use n = 144 Dose: 1500mg Frequency: Once daily Duration: 12 months	<u>Total knee replacement:</u> Follow-Up Time: 5 years : Comparator: Arm 2 vs Arm 1 , RR : 0.43 95% CI: (0.20, 0.92)
Cakir, 2014[79] Study design: RCT Trial name: None Study Location: Turkey Health care setting: Department of Physical Medicine and Rehabilitation Single Site	Total n = 60 Age Range: 40-80 Arm 1, Mean Age: 57.1 (7.8) BMI: 29.5 (5.9) Arm 2, Mean Age: 56.9 (8.8) BMI: 27.9 (4.4) Arm 3, Mean Age: 58.2 (9.9) BMI: 30.9 (4.0) Female: 15.5% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: 2&3, ACR Analgesic Use: Yes, Paracetamol up to 2000 mg/day	Diagnosis of osteoarthritis of the knee Duration of Symptoms: 6 months Minimum Age: 40 Maximum Age:79 K-L: 2&3	Concomitant medical problems that prevent participation Concomitant or prior use of other meds Injected hyaluronic acid in the past or during the past 6 month(s) Injected corticosteroids in the prior 1 month(s) Physical Therapy or Rehab or exercise in the previous month(s) Prior experience with the intervention of interest Joint infection, neoplasm, diabetes mellitus, paresis, osteonecrosis, recent trauma, ascertained/suspected pregnancy or lactating and poor general health status	Arm 1: Control n = 20 Placebo/Sham procedure Frequency: 5 times a week Duration: 12 months Co-Intervention: Isometric exercise, strengthening, stretching Arm 2: Continuous Ultrasound n = 20 Dose: Frequency of 1 MHz with intensity of 1 W/cm2 Frequency: 5 times a week Duration: 12 months Co-Intervention: Isometric exercise, strengthening, stretching Arm 3: Pulse Ultrasound n = 20 Dose: Frequency of 1 MHz with intensity of 1 W/cm2 Frequency: 5 times a week Duration: 12 months Co-Intervention: Isometric exercise, strengthening, stretching	<u>VAS pain at rest:</u> Follow-Up Time: 6.5 months : Comparator: Arm 2 vs Arm 1 , MD : -0.90 95% CI: (-11.14, 9.34) Comparator: Arm 3 vs Arm 1 , MD : -2.10 95% CI: (-10.99, 6.79) <u>VAS pain on movement:</u> Follow-Up Time: 6.5 months : Comparator: Arm 2 vs Arm 1 , MD : 0.60 95% CI: (-13.56, 14.76) Comparator: Arm 3 vs Arm 1 , MD : -0.60 95% CI: (-16.69, 15.49) <u>WOMAC function:</u> Follow-Up Time: 6.5 months : Comparator: Arm 2 vs Arm 1 , MD : -2.90 95% CI: (-9.15, 3.35) Comparator: Arm 3 vs Arm 1 , MD : 1.60 95% CI: (-2.94, 6.14) <u>WOMAC pain:</u> Follow-Up Time: 6.5 months : Comparator: Arm 2 vs Arm 1 , MD : -1.60 95% CI: (-3.25, 0.05) Comparator: Arm 3 vs Arm 1 , MD : 0.20 95% CI: (-1.32, 1.72)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Callaghan, 2015[100] Study design: RCT Trial name: None Study Location: UK Health care setting: NR Single Site	Total n = 126 Age Range: 40-70 Arm 1, Mean Age: 56.4 (8.1) BMI: 30.5 (5.1) Arm 2, Mean Age: 54.5 (6.7) BMI: 31.4 Female: 57.1 Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: Patellofemora 100% Diagnosis: K-L: 2&3 Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: 3 months; >=4 on VAS scale Taking same medication for past 3 months K-L: 2&3 Patellofemoral OA: PL OA is present and greater than tibiofemoral OA	Concomitant medical problems that prevent participation Prior surgery on one or both knees Injected corticosteroids in the prior 1 month(s) Initiating new treatment	Arm 1: No brace n = 63 Placebo/Control Duration: 6 weeks Method of Blinding: Single-blind Arm 2: Brace n = 63 Duration: 6 weeks Method of Blinding: Single-blind	<u>Koos pain subscale:</u> Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -5.70 95% CI: (-10.76, -0.64) <u>VAS:</u> Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.30 95% CI: (-2.01, -0.59)
Campos, 2015[106] Study design: RCT Trial name: None Study Location: Brazil Health care setting: Hospital-outpatient Single Site	Total n = 58 Mean Age: 64.3 Arm 1, Mean Age: 63.3 (7.5) BMI: 30.3 (5.1) Arm 2, Mean Age: 65.2 (9.6) BMI: 30.8 (6.1) Female: 63.8 Racial/Ethnic Distribution: African American 10.3%, Asian 3.4%, Caucasian 74.1%, 12.1% Mixed Living Situation: NR Location of OA: NR Subtype: Medial 100% Diagnosis: K-L: 1-4, ACR Analgesic Use: Yes, Unlimited	Diagnosis of osteoarthritis of the knee Duration of Symptoms: 6 months of usual care treatment Able to sign Consent ACR	Concomitant medical problems that prevent participation Pending surgery Concomitant or prior use of other meds	Arm 1: Neutral insole n = 29 Placebo/Sham Dose: 5-10 hrs/day Frequency: Daily Duration: 6 months Method of Blinding: Unblinded Arm 2: Wedged insole n = 29 Dose: 5-10 hrs/day Frequency: Daily Duration: 6 months Method of Blinding: Unblinded	<u>Lequesne index:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : 1.10 95% CI: (-1.19, 3.39) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : 1.00 95% CI: (-1.02, 3.02) <u>VAS:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.20 95% CI: (-14.34, 9.94) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.30 95% CI: (-11.99, 11.39) <u>WOMAC pain:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.10 95% CI: (-2.30, 2.10) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.70 95% CI: (-2.64, 1.24) <u>WOMAC total:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.70 95% CI: (-13.38, 7.98) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.00 95% CI: (-11.04, 9.04)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Carlos, 2012[80] Study design: RCT Trial name: None Study Location: Brazil Health care setting: Physical therapy outpatient clinic Single Site	Total n = 30 Arm 1, Mean Age: 62.7(8.7) BMI: 31.1(3.2) Arm 2, Mean Age: 63.4(4.6) BMI: 27.8(3.8) Arm 3, Mean Age: 63.9(6.3) BMI: 31.8(4.1) Female: 70% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: bilateral 86.7%, unilateral 13.3% Subtype: NR Diagnosis: K-L: Grade I1-4 on at least one knee Analgesic Use: No	Diagnosis of osteoarthritis of the knee Duration of Symptoms: 3 months Minimum Age: 50 Maximum Age:75 K-L:-grade I1-4	Concomitant medical problems that prevent participation Continued Use of Analgesics Diabetes, uncontrolled hypertension, morbid obesity Dementia OA of the hip Use of anti-inflammatory or anxiolytic drugs during the past 6 months	Arm 1: Exercise n = 10 Dose: 45 minutes (2 sets of 30 reps) Frequency: 3 sessions per week Duration: 8 weeks Arm 2: Ultrasound n = 10 Dose: 2.5W/cm2, 20%, 100Hz Frequency: 3 sessions per week for 4 weeks Duration: 8 weeks (4 weeks US, 4 weeks exercise) Co-Intervention: strength/resistance training 3 sessions per week for 4 weeks Arm 3: Ultrasound n = 10 Dose: Frequency: 3 sessions per week for 4 weeks Duration: 8 weeks (4 weeks US, 4 weeks exercise) Co-Intervention: strength/resistance training 3 sessions per week for 4 weeks	<u>VAS movement:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.05 95% CI: (-0.23, 0.14) Comparator: Arm 3 vs Arm 1 , MD : 0.03 95% CI: (-0.08, 0.14) <u>VAS rest:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.42 95% CI: (0.13, 0.71) Comparator: Arm 3 vs Arm 1 , MD : 0.17 95% CI: (-0.17, 0.50) <u>WOMAC function:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.38 95% CI: (0.16, 0.60) Comparator: Arm 3 vs Arm 1 , MD : 0.31 95% CI: (0.08, 0.54) <u>WOMAC pain:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.42 95% CI: (0.25, 0.59) Comparator: Arm 3 vs Arm 1 , MD : 0.32 95% CI: (0.09, 0.55) <u>WOMAC total:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.43 95% CI: (0.15, 0.71) Comparator: Arm 3 vs Arm 1 , MD : 0.28 95% CI: (-0.01, 0.57)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Cheawthamai, 2014[117] Study design: RCT Trial name: None Study Location: Thailand Health care setting: Academic physical therapy department Single Site	Total n = 43 Age Range: 65.3 Arm 1, Mean Age: 64.1(7.9) BMI: 27.1(3.6) Arm 2, Mean Age: 66.6(8.8) BMI: 27.0(4.6) Female: 100% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: bilateral 51%, unilateral 48% Subtype: NR Diagnosis: ACR Analgesic Use: Yes, Participants were instructed to continue any current medication and not to start any new medication	Diagnosis of osteoarthritis of the knee Female ACR: NR	Surgery knee limb in prior 1.5 months month(s) Injected corticosteroids in the prior 1month month(s) Systemic joint disease, cerebrovascular disease, Parkinson's Back and limb surgery in the prior 1.5 months	Arm 1: Home-exercise program n = 22 Placebo/Home-exercise Dose: Customized Frequency: Daily Duration: 12 weeks Arm 2: Manipulation/manual therapy n = 21 Dose: Customized Frequency: Daily Duration: 12 weeks Co-Intervention: home-based exercise	<u>6 min walk (meter):</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : 5.00 95% CI: (NC, NC) Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : 10.00 95% CI: (NC, NC) <u>VAS pain:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.20 95% CI: (-1.29, 1.69) Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : 1.90 95% CI: (0.41, 3.39)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Cherian, 2015[101] Study design: RCT Trial name: None Study Location: US Health care setting: NR Single Site	Total n = 52 Age Range: 41-80 Arm 1, Mean Age: 54 Arm 2, Mean Age: 59 Female: 48.1% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: 3&4 Analgesic Use: Yes, Both treatment and the matched cohorts were not prohibited from receiving previously prescribed NSAIDs. However, we instructed patients to remain taking the same dosage of NSAIDs medication throughout the study, and that if increase or change of dosage was needed, this would only occur after their three month follow-up appointment. In addition, no patients in the study were started on new pain medications at the time of enrollment and throughout the trial period by our institution. The rationale behind our choices for a corticosteroid injection/ physical therapy and to allow the use of NSAID as the matching cohort was to compare the use of the brace to the current initial standard of care at our institution.	Diagnosis of osteoarthritis of the knee Minimum Age: 41 Maximum Age:79 Able to sign Consent Medial or lateral OA Persistent pain beyond treatment Ability to comply with treatment K-L: 3&4	Concomitant medical problems that prevent participation Surgery knee limb in prior 6 month(s) Injected corticosteroids in the prior 3 month(s) Equal medial/lateral OA History of traumatic onset of knee pain	Arm 1: Usual care n = 26 Placebo/Usual care Dose: 1 mL Kenalog 40 mg and 4 mL of 1% lidocaine (corticosteroids); unspecified length of time (physical therapy) Frequency: Unspecified (corticosteroids); gait training three times a week for six weeks, self-directed physical therapy every other day (physical therapy) Duration: 3 months Method of Blinding: Single-blinded Arm 2: Brace n = 26 Dose: 3+ hrs per day Frequency: Daily Duration: 3 months Method of Blinding: Single-blinded	<u>SF-36 mental:</u> Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -2.30 95% CI: (NC, NC) <u>SF-36 physical:</u> Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : 5.90 95% CI: (NC, NC) <u>TUG (s):</u> Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -3.10 95% CI: (NC, NC) <u>VAS:</u> Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -2.30 95% CI: (-3.66, -0.94)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Cheung, 2014[71] Study design: RCT Trial name: None Study Location: US Health care setting: Home, NR Site size: NR	Total n = 36 Mean Age: 72 Arm 1, Mean Age: 71.9 (69.3, 74.6) 95% CI BMI: 29.1 (26.7, 31.7) 95% CI Arm 2, Mean Age: 71.9 (69.0, 75.0) 95% CI BMI: 28.8 (26.0, 31.7) 95% CI Female: 100% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: ACR Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: 6 months Minimum Age: 65 Maximum Age:89 ACR	Concomitant medical problems that prevent participation Surgery knee limb in prior 24 month(s) Injected hyaluronic acid in the past or during the past 6 month(s) Injected corticosteroids in the prior 3 month(s) Prior experience with the intervention of interest Not currently participating in a supervised exercise program Cognitive/mental impairment Symptoms of joint locking; in stability indicated by chronic use of a knee brace, cane, walker, or wheelchair Prior joint replacement : a) uncontrolled high blood pressure or existing heart condition; and b) other comorbid condition with overlapping symptoms (i.e. fibromyalgia, rheumatoid arthritis) were also be excluded.	Arm 1: Wait list control n = 18 Placebo/Wait list Duration: 8 weeks Method of Blinding: Single-blind Arm 2: Hatha yoga n = 18 Dose: 60 minutes Frequency: Weekly Duration: 8 weeks Method of Blinding: Single-blind	<u>SF-12 mental component:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : 2.00 95% CI: (-1.33, 5.33) <u>SF-12 physical component:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.70 95% CI: (-2.04, 3.44) <u>WOMAC function:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -4.20 95% CI: (-10.58, 2.18) <u>WOMAC pain:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.50 95% CI: (-4.36, -0.64) <u>WOMAC total:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -8.30 95% CI: (-16.62, 0.02)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Christensen, 2015[62] Study design: RCT Trial name: CAROT Study Location: Denmark Health care setting: Home, Hospital-outpatient, Dietary unit Site size: NR	Total n = 192 Total # of knees = NR Age Range: NR Arm 1, Mean Age: 61.7 (SD 6.8) BMI: NR Arm 2, Mean Age: 63.0 (SD 6.5) BMI: NR Arm 3, Mean Age: 62.9 (SD 5.8) BMI: NR Female: 80.7% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: bilateral 89%, unilateral 11% Subtype: NR Diagnosis: Confirmed knee OA based on clinical symptoms, including pain, and on standing radiographs in at least 1 joint compartment Analgesic Use: Yes, Participants were asked not to change any medication or nutritional supplements during the study	Diagnosis of osteoarthritis of the knee Minimum Age: 50 BMI >= 30 kg/m2 NR: Confirmed knee OA based on clinical symptoms, including pain, and on standing radiographs in at least 1 joint compartment	Pending surgery Lack of motivation to lose weight Inability to speak Danish Planned antiobesity surgery, total knee alloplasty (TKA), or receiving pharmacologic therapy for obesity	Arm 1: Control n = 64 Placebo/Control Dose: NA Frequency: NA Duration: 68 weeks (16 on co-intervention, 52 on control) Method of Blinding: NR Co-Intervention: Initial 16-week intensive dietary therapy Arm 2: Weight loss n = 64 Dose: 1 hour sessions Frequency: Weekly sessions for 52 weeks Duration: 68 weeks (16 on co-intervention, 52 on additional weight loss intervention) Method of Blinding: NR Co-Intervention: Initial 16-week intensive dietary therapy Arm 3: Home exercise program; strength/resistance training n = 64 Dose: 60 minutes per session Frequency: 3 days per week Duration: 68 weeks (16 on co-intervention, 52 on additional exercise intervention) Method of Blinding: NR Co-Intervention: Initial 16-week intensive dietary therapy	<u>6 min walk (meter):</u> Follow-Up Time: 68 weeks : Comparator: Arm 2 vs Arm 1 , MD : -14.63 95% CI: (-35.67, 6.41) Comparator: Arm 3 vs Arm 1 , MD : -15.59 95% CI: (-36.63, 5.45) <u>KOOS pain:</u> Follow-Up Time: 68 weeks : Comparator: Arm 2 vs Arm 1 , MD : 1.10 95% CI: (-4.13, 6.33) Comparator: Arm 3 vs Arm 1 , MD : 1.90 95% CI: (-3.33, 7.13) <u>SF-36 mental health:</u> Follow-Up Time: 68 weeks : Comparator: Arm 2 vs Arm 1 , MD : 1.60 95% CI: (-1.09, 4.29) Comparator: Arm 3 vs Arm 1 , MD : 1.20 95% CI: (-1.49, 3.89) <u>SF-36 physical component:</u> Follow-Up Time: 68 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.10 95% CI: (-3.86, 1.66) Comparator: Arm 3 vs Arm 1 , MD : 0.60 95% CI: (-2.16, 3.36) <u>VAS pain:</u> Follow-Up Time: 68 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.60 95% CI: (-7.67, 6.47) Comparator: Arm 3 vs Arm 1 , MD : -0.10 95% CI: (-7.17, 6.97) <u>Change in BMI:</u> Follow-Up Time: 68 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.10 95% CI: (-2.09, -0.11) Comparator: Arm 3 vs Arm 1 , MD : 0.60 95% CI: (-0.39, 1.59)
Christensen, 2015[62] -Continued					<u>Weightloss, kg:</u> Follow-Up Time: 68 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.73 95% CI: (-5.37, -0.09) Comparator: Arm 3 vs Arm 1 , MD : 1.99 95% CI: (-0.65, 4.63)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Claes, 2015[130] Study design: Single arm trial Trial name: Osteoarthritis Chronic CAre Program (OACCP) Study Location: Australia Health care setting: Hospital-outpatient Multiple Sites: 11	Total n = 203 Arm 1, Mean Age: 67.3(9.7) BMI: 31.3(6.6) Female: 64.5 Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: VAS >=4/10 at initial assessment; waiting list for TKR or orthopaedic referral	VAS>=4/10 at recruitment visit Pain associated with affected joint on most days of prior month	Exclusion : NR	Arm 1: Weight loss n = 203 Placebo/NA Dose: NA Frequency: NA Duration: 1 year Method of Blinding: NA Co-Intervention: NA	<u>6-minute walk test (m):</u> Follow-Up Time: 12 weeks : Comparator: post-pre , MD : 36.70 95% CI: (27.2, 46.2) Follow-Up Time: 26 weeks : Comparator: post-pre , MD : 44.00 95% CI: (31.5, 56.5) <u>BMI:</u> Follow-Up Time: 12 weeks : Comparator: pre-post , MD : 0.50 95% CI: (0.3, 0.7) Follow-Up Time: 26 weeks : Comparator: pre-post , MD : 0.80 95% CI: (0.5, 1.1) <u>KOOS pain:</u> Follow-Up Time: 12 weeks : Comparator: post-pre , MD : 5.00 95% CI: (2.0, 7.9) Follow-Up Time: 26 weeks : Comparator: post-pre , MD : 5.60 95% CI: (1.6, 9.6) <u>TUG (s):</u> Follow-Up Time: 12 weeks : Comparator: pre-post , MD : 1.40 95% CI: (1.1, 1.7) Follow-Up Time: 26 weeks : Comparator: pre-post , MD : 2.00 95% CI: (1.4, 2.6) <u>VAS pain:</u> Follow-Up Time: 12 weeks : Comparator: pre-post , MD : 1.00 95% CI: (0.7, 1.3) Follow-Up Time: 26 weeks : Comparator: pre-post , MD : 0.90 95% CI: (0.4, 1.4)
Claes, 2015[130] - Continued					<u>Weight (kg):</u> Follow-Up Time: 12 weeks : Comparator: pre-post , MD : 1.40 95% CI: (0.8, 2.0) Follow-Up Time: 26 weeks : Comparator: pre-post , MD : 2.10 95% CI: (1.2, 3.0)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Coleman, 2012[133] Study design: RCT Trial name: Osteoarthritis of the Knee Self Management Program Study Location: Australia Health care setting: Community venue Site size: NR	Total n = 146 Total # of knees = NR Mean Age(SD): 65 (SD 8) Arm 1, Mean Age: 65 (SD 8.7) BMI: NR Arm 2, Mean Age: 65 (SD 7.9) BMI: NR Female: 74.7% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: X-ray or clinical diagnosis of OA Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: 18 English-speaking Referral from general practitioner or specialist Able to meet program requirements NR: X-ray or clinical diagnosis of OA	Concomitant medical problems that prevent participation Surgery knee limb in prior 6 month(s) Coexisting inflammatory arthritis Serious comorbidity Knee replacement scheduled in < 6 months Cannot meet program time points	Arm 1: Control group n = 75 Placebo/Control Dose: NA Frequency: NA Duration: 6 weeks Method of Blinding: Patients were not blind, physiotherapists performing the assessments were blind to group allocation Co-Intervention: NR Arm 2: Self-management program n = 71 Dose: 2.5 hours Frequency: Once per week Duration: 6 weeks Method of Blinding: Patients were not blind, physiotherapists performing the assessments were blind to group allocation Co-Intervention: NR	<u>SF-36 body pain:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -6.00 95% CI: (-11.96, -0.04) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -7.20 95% CI: (-12.47, -1.93) <u>SF-36 physical function:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -5.70 95% CI: (-10.97, -0.43) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -5.60 95% CI: (-9.48, -1.72) <u>TUG (s):</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -1.00 95% CI: (-1.55, -0.45) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.00 95% CI: (-1.55, -0.45) <u>WOMAC function:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -3.50 95% CI: (-6.14, -0.86) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -5.30 95% CI: (-7.24, -3.36) <u>WOMAC pain:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -0.60 95% CI: (-1.43, 0.23) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.50 95% CI: (-2.33, -0.67) <u>WOMAC total:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -4.10 95% CI: (-7.43, -0.77)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Coleman, 2012[133] - Continued					Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -7.20 95% CI: (-9.97, -4.43) <u>Number with MCII SF36 pain:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , RR : 0.81 95% CI: (0.54, 1.21) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , RR : 0.73 95% CI: (0.43, 1.24) <u>Number with MCII SF36 physical function:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , RR : 0.73 95% CI: (0.52, 1.02) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , RR : 0.57 95% CI: (0.38, 0.84) <u>Number with MCII TUG:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , RR : 0.68 95% CI: (0.47, 0.99) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , RR : 0.32 95% CI: (0.20, 0.52) <u>Number with MCII VAS Pain:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , RR : 0.20 95% CI: (0.08, 0.49) <u>Number with MCII WOMAC physical function:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , RR : 0.56 95% CI: (0.33, 0.95) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , RR : 0.24 95% CI: (0.11, 0.51)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Cortes, 2014[118] Study design: RCT Trial name: None Study Location: Spain Health care setting: NR Site size: NR	Total n = 18 Total # of knees = NR Age Range: 67-91 Arm 1, Mean Age: NR BMI: NR Female: NR Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: Radiologic evidence and/or clinical signs of knee OA Analgesic Use: Yes, No changes in drug administration, including NSAIDs, during the study	Able to sign Consent Knee pain most days within the last month Disabling knee pain during at least one of the following activities: going down stairs or upstairs; walking at a pace of 0.4 km; and standing up or sitting down on the toilet or bed No changes in drug administration, including NSAIDs, during the study	Concomitant medical problems that prevent participation Surgery knee limb in prior 12 month(s) Injected hyaluronic acid in the past or during the past 6 month(s) Injected corticosteroids in the prior 6 month(s) Rheumatoid arthritis or other inflammatory joint disease Intra-articular injection within the last 6 months Cognitive impairment that may bias the research	Arm 1: Control n = 9 Placebo/Control Dose: NA Frequency: NA Duration: 6 weeks Method of Blinding: Arm 2: Massage	<u>TUG (s):</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : 3.94 95% CI: (-4.01, 11.89) Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : 2.84 95% CI: (-4.61, 10.29) <u>VAS pain:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : 3.10 95% CI: (0.76, 5.44) Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : 2.28 95% CI: (0.44, 4.12) <u>WOMAC total:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : 21.42 95% CI: (9.79, 33.05) Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : 14.04 95% CI: (4.71, 23.37)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
da Silva, 2015[58] Study design: RCT Trial name: None Study Location: Brazil Health care setting: Physical therapy outpatient clinic Single Site	Total n = 30 Mean Age: 59 Arm 1, Mean Age: 60 ± 7.76 BMI: 29.29 ± 5.00 Arm 2, Mean Age: 57 ± 6.01 BMI: 29.37 ± 4.10 Female: 87% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: Lequesne, ACR Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: 18 Pain within the past year; on most days for at least 3 months Stable doses of NSAIDs ACR: NA Lequesne Index: 5-13	Concomitant medical problems that prevent participation Prior experience with the intervention of interest Other cause of pain in the lower limb Refusal to continue Two consecutive or 3 non-consecutive absences	Arm 1: Control n = 15 Duration: 8 weeks Co-Intervention: Pre-randomization self-management program Arm 2: Land-based exercise program n = 15 Dose: 45 minutes per session Frequency: 2 sessions per week Duration: 8 weeks Co-Intervention: Pre-randomization self-management program plus weekly educational sessions	<u>6 min walk:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -50.40 95% CI: (-94.26, -6.54) <u>Lequesne Index Function:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.83 95% CI: (-1.84, 0.18) <u>SF-36 bodily pain:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -14.80 95% CI: (-27.39, -2.21) <u>SF-36 physical function:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -14.00 95% CI: (-26.24, -1.76) <u>SF-36 role physical:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -53.33 95% CI: (-76.10, -30.56) <u>TUG (s):</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.05 95% CI: (-3.12, -0.98)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
de Rooij, 2016[66] Study design: RCT Trial name: None Study Location: Netherlands Health care setting: Secondary outpatient rehabilitation center Single Site	Total n = 126 Arm 1, Mean Age: 63.9 (12.4) BMI: 35 (7.6) Arm 2, Mean Age: 63.2 (8.4) BMI: 36 (6.8) Female: 77% T, 73% C Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: bilateral 19%, unilateral 81% Subtype: NR Diagnosis: K-L: 0-IV, ACR Analgesic Use: Yes, 79.4% T/76.2% C use pain meds	Diagnosis of osteoarthritis of the knee Presence of coronary disease, HF, type 2 diabetes, COPD, or obesity, Primary treatment goal related to OAK ACR: diagnosis of OAK	Concomitant medical problems that prevent participation Pending surgery Prior experience with the intervention of interest Insufficient knowledge of Dutch Psych distress necessitating treatment Dementia; MMSE>25 Expected to be lost at follow up (i.e. moving) Refusal to sign informed consent	Arm 1: Usual care / waitlist n = 63 Placebo/Usual care / waitlist Duration: 32 weeks on waitlist Arm 2: Exercise therapy n = 63 Dose: 30-60 min Frequency: Twice a week Duration: 20 weeks	<u>6MWT:</u> Follow-Up Time: 10 weeks : Comparator: Arm 2 vs Arm 1 , MD : -17.20 95% CI: (-56.64, 22.24) Follow-Up Time: 20 weeks : Comparator: Arm 2 vs Arm 1 , MD : -31.50 95% CI: (-71.82, 8.82) Follow-Up Time: 32 weeks : Comparator: Arm 2 vs Arm 1 , MD : -42.30 95% CI: (-82.63, -1.97) <u>NRS pain:</u> Follow-Up Time: 10 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.40 95% CI: (-1.17, 0.37) Follow-Up Time: 20 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.50 95% CI: (-2.26, -0.74) Follow-Up Time: 32 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.50 95% CI: (-2.26, -0.74) <u>SF-36 physical health:</u> Follow-Up Time: 20 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.90 95% CI: (-3.62, -0.18) Follow-Up Time: 32 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.50 95% CI: (-4.26, -0.74) <u>TUG:</u> Follow-Up Time: 10 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.90 95% CI: (-2.32, 0.52) Follow-Up Time: 20 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.10 95% CI: (-2.57, 0.37) Follow-Up Time: 32 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.40 95% CI: (-2.69, -0.11)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
de Rooij, 2016[66] - Continued					<u>WOMAC function:</u> Follow-Up Time: 10 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.50 95% CI: (-6.67, 1.67) Follow-Up Time: 20 weeks : Comparator: Arm 2 vs Arm 1 , MD : -5.10 95% CI: (-9.81, -0.39) Follow-Up Time: 32 weeks : Comparator: Arm 2 vs Arm 1 , MD : -7.90 95% CI: (-12.78, -3.02) <u>WOMAC pain:</u> Follow-Up Time: 10 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.70 95% CI: (-1.92, 0.52) Follow-Up Time: 20 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.90 95% CI: (-3.28, -0.52) Follow-Up Time: 32 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.00 95% CI: (-3.37, -0.63)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Dundar, 2015[91] Study design: RCT Trial name: None Study Location: Turkey Health care setting: Academic Physical Medicine and Rehabilitation Department Single Site	Total n = 40 Total # of knees = NR Age Range: NR Arm 1, Mean Age: 57.6 BMI: 31.2 Arm 2, Mean Age: 56.8 BMI: 31.7 Female: 72.5% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: bilateral 100% Subtype: NR Diagnosis: K-L: 2&3, Bilateral knee OA diagnosis according to ACR criteria Analgesic Use: Yes, Patients were not allowed to change the dosage of their routine pain medication or begin a new pain medication during the study.	Inclusion : NR	Concomitant medical problems that prevent participation Surgery knee limb in prior 6 month(s) Injected hyaluronic acid in the past or during the past 6 month(s) Injected corticosteroids in the prior 6 month(s) Pregnant Not allowed to change dosage of their routine pain medication Not allowed to begin new pain medication	Arm 1: Sham Procedure n = 20 Placebo/Sham Procedure Dose: NR Frequency: 5 times per week Duration: 4 weeks Method of Blinding: The WOMAC questionnaire and VAS for pain were performed by a physiatrist who was blind to the patient's treatment protocol. Another clinician blinded to the patient's clinical and treatment data, performed the ultrasound. Co-Intervention: Both groups received 20 sessions (5 sessions in a week, each lasting 60 min) of physical therapy, including hot pack, ultrasound, TENS and isometric knee exercise Arm 2: Neuromuscular electrical stimulation n = 20 Dose: frequency of 50Hz, intensity 100 microT for 20 minutes Frequency: 5 times per week Duration: 4 weeks Method of Blinding: The WOMAC questionnaire and VAS for pain were performed by a physiatrist who was blind to the patient's treatment protocol. Another clinician blinded to the patient's clinical and treatment data, performed the ultrasound. Co-Intervention: Both groups received 20 sessions (5 sessions in a week, each lasting 60 min) of physical therapy, including hot pack, ultrasound, TENS and isometric knee exercise	<u>Total WOMAC:</u> Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : 7.00 95% CI: (NC, NC) <u>VAS pain:</u> Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.00 95% CI: (-15.49, 15.49) <u>WOMAC pain:</u> Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : 7.00 95% CI: (NC, NC)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Dwyer, 2015[120] Study design: RCT Trial name: None Study Location: US, South Africa Health care setting: Chiropractic university-based outpatient teaching clinics Multiple Sites: 2	Total n = 78 Total # of knees = 85 Age Range: 38-80 Arm 1, Mean Age: 60.9 (10.3) BMI: 28.6 (5.2) Arm 2, Mean Age: 63.5 (10.9) BMI: 28.6 (5.2) Arm 3, Mean Age: 62.2 (11.8) BMI: 30.6 (7.6) Female: 63 Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: bilateral 91%, unilateral 9% Subtype: NR Diagnosis: K-L: 0-3, of three clinical criteria involving knee pain, crepitus, morning stiffness, and bony enlargement Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: >=1 year Minimum Age: 38 Maximum Age:79 Ambulatory K-L: 0-3 1 of three clinical criteria involving knee pain, crepitus, morning stiffness, and bony enlargement: 1 of 3 criteria	Surgery knee limb in prior 6 month(s) Prior experience with the intervention of interest >=720/2400 on WOMAC	Arm 1: Rehabilitation n = 26 Placebo/Usual care Dose: 20 min Frequency: 6 times Duration: 4 weeks Method of Blinding: Unblinded Arm 2: Manual and manipulative therapy (MMT) n = 26 Dose: 20 minutes Frequency: 12 times Duration: 4 weeks Method of Blinding: Unblinded Arm 3: Rehabilitation + Manual and manipulative therapy (MMT) n = 26 Dose: 20-40 minutes Frequency: 6 session ß- 3 with extra training Duration: 4 weeks Method of Blinding: Unblinded Co-Intervention: Rehab or MMT	<u>WOMAC function:</u> Follow-Up Time: 5 weeks : Comparator: Arm 2 vs Arm 1 , MD : -22.00 95% CI: (-162.58, 118.58) Comparator: Arm 3 vs Arm 1 , MD : -32.80 95% CI: (-191.40, 125.80) <u>WOMAC pain:</u> Follow-Up Time: 5 weeks : Comparator: Arm 2 vs Arm 1 , MD : -26.90 95% CI: (-68.88, 15.08) Comparator: Arm 3 vs Arm 1 , MD : -31.50 95% CI: (-72.40, 9.40) <u>WOMAC total:</u> Follow-Up Time: 5 weeks : Comparator: Arm 2 vs Arm 1 , MD : -80.50 95% CI: (-281.64, 120.64) Comparator: Arm 3 vs Arm 1 , MD : -63.20 95% CI: (-273.72, 147.32)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Elboim-Gabyzon, 2013[85] Study design: RCT Trial name: None Study Location: Israel Health care setting: Physical therapy outpatient clinic Single Site	Total n = 63 Mean Age(SD): 68.9 (SD 7.7) Arm 1, Mean Age: NR BMI: NR Arm 2, Mean Age: NR BMI: NR Female: 82.5% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: >=2, Diagnosis of idiopathic knee OA Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: Knee pain at least 3 months, with pain presenting at least three days a week during the last month Minimum Age: 51 Ambulatory Ability to follow instructions K-L: >=2 ACR: Compliance with the classification of ACR NR: Diagnosis of idiopathic knee OA	Concomitant medical problems that prevent participation Prior surgery on one or both knees Injected hyaluronic acid in the past or during the past 6 month(s) Injected corticosteroids in the prior 6 month(s) Existence of a pacemaker History of cardiovascular, neurological or orthopedic problems that could affect functional performance or previous knee surgery other than arthroscopy Inability to tolerate electrical stimulation at a level of current sufficient to elicit full knee extension Change in pain medication in the previous month Injections to the knee joint during the previous six months	Arm 1: Control n = 30, Placebo/Control, Dose: NA, Frequency: NA, Duration: NA Method of Blinding: Assessor was blind to treatment allocation only at the initial assessment. Physical therapists leading group exercise program were familiar with the study protocol were not aware of treatment allocation. Co-Intervention: Group exercise program consisting of 12 45-minute sessions, biweekly for six weeks, with 6–8 subjects in each group led by one of 3 physical therapists. To be included in final analysis, subjects had to complete the 12 sessions within 8 weeks. The program included: range of motion exercises; knee and lower extremity muscle-strengthening exercises; functional activities; and balance training. Sessions also included patient education on self-management; activity and exercise planning, and discussion of pain-coping strategies. Arm 2: Neuromuscular electrical stimulation n = 33, Dose: 75 Hz frequency; 2s ramp-up time; 10s on time; 2s off time; amplitude to tolerance (max 100mA); 10 contractions, Frequency: Biweekly, Duration: 6 weeks Method of Blinding: Assessor was blind to treatment allocation only at the initial assessment. Physical therapists leading group exercise program were familiar with the study protocol were not aware of treatment allocation. Co-Intervention: Group exercise program consisting of 12 45-minute sessions, biweekly for six weeks, with 6–8 subjects in each group led by one of 3 physical therapists. To be included in final analysis, subjects had to complete the 12 sessions within 8 weeks.	<u>TUG (s):</u> Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.20 95% CI: (-1.60, 2.00) <u>VAS pain:</u> Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.70 95% CI: (-2.98, -0.42) <u>WOMAC total:</u> Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -23.20 95% CI: (-49.20, 2.80)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Elboim-Gabyzon, 2013[85] -Continued				The program included: range of motion exercises; knee and lower extremity muscle-strengthening exercises; functional activities; and balance training. Sessions also included patient education on self-management; activity and exercise planning, and discussion of pain-coping strategies.	
Erhart, 2010[113] Study design: RCT Trial name: None Study Location: US Health care setting: NR Site size: NR	Total n = 79 Total # of knees = NR Age Range: >=60.2 Arm 1, Mean Age: 62.1 BMI: 27.4 Arm 2, Mean Age: 61.4 BMI: 27.6 Female: 51.39% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: Medial 100% Diagnosis: Osteoarthritic changes based on MRI (cartilage thinning and/or osteophytes) Analgesic Use: NR	Minimum Age: 40 Maximum Age:79 Ambulatory Able to sign Consent	Concomitant medical problems that prevent participation Prior surgery on one or both knees Concomitant or prior use of other meds Prior acute injury to the knee BMI >35 kg/m2 Use of shoe insert or hinged knee brace Narcotic pain medication use Intraarticular joint injection in previous 2 months Nerve or muscle disease associated with walking difficulty, Gout or recurrent pseudogout, and Diagnosed or symptomatic osteoarthritis in other lower extremity joints, and Serious injury to foot, ankle, back, or hips	Arm 1: Control n = 26 Placebo/Control shoes Dose: NA Frequency: Suggested minimum wear time 4hr/day, average monthly reports 7.9-9.5h/day Duration: 6 months Method of Blinding: Subjects were blinded to the shoe type, researcher was not blinded Co-Intervention: NR Arm 2: Variable-stiffness shoes n = 34 Dose: NA Frequency: Suggested minimum wear time 4hr/day, average monthly reports 6.9-8.0h/day Duration: 6 months Method of Blinding: Subjects were blinded to the shoe type, researcher was not blinded Co-Intervention: NR	<u>WOMAC pain:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -3.70 95% CI: (-10.08, 2.68) <u>WOMAC total:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -10.00 95% CI: (-36.46, 16.46) <u>Clinically significant on WOMAC pain:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , RR : 0.49 95% CI: (0.31, 0.79)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Erhart-Hledik, 2012[114] Study design: RCT Trial name: None Study Location: NR Health care setting: NR Site size: NR	Total n = 79 Total # of knees = NR Mean Age(SD): 60.2 (SD 9.8) Arm 1, Mean Age: 61.0 (SD 12.0) BMI: NR Arm 2, Mean Age: 57.3 (SD 8.5) BMI: NR Female: 46.8% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: Medial 100% Diagnosis: Symptomatic medial compartment knee OA, osteoarthritic changes based on MRI/radiograph Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: Persistent medial compartment knee joint pain Minimum Age: 40 Maximum Age:80 Ambulatory Able to sign Consent NR: Symptomatic medial compartment knee OA NR: Osteoarthritic changes based on MRI/radiograph	Concomitant medical problems that prevent participation Prior surgery on one or both knees Concomitant or prior use of other meds Injected hyaluronic acid in the past or during the past 2 month(s) Injected corticosteroids in the prior 2 month(s) Prior acute injury to the knee BMI > 35 kg/m2 Total knee replacement Intraarticular joint injection in previous 2 months Use of shoe insert or hinged knee brace or narcotic pain medication Nerve or muscle disease associated with walking difficulty; serious injury to foot, ankle, back, or hips; gout or recurrent pseudogout; or OA in other lower extremity joint	Arm 1: Control n = 39 Placebo/Control, constant-stiffness shoe Dose: Instructed to use their assigned shoes as their main walking shoes, a minimum 4 h of wear per day Frequency: Daily Duration: 12 months Method of Blinding: Patients were blinded to their shoe type. The researcher performing the gait analysis was not blinded to shoe type. Co-Intervention: NR Arm 2: Orthotics/shoes n = 40 Dose: Instructed to use their assigned shoes as their main walking shoes, a minimum 4 h of wear per day Frequency: Daily Duration: 12 months Method of Blinding: Patients were blinded to their shoe type. The researcher performing the gait analysis was not blinded to shoe type. Co-Intervention: NR	<u>WOMAC pain:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -1.00 95% CI: (NC, NC)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Fioravanti, 2012[72] Study design: RCT Trial name: None Study Location: Italy Health care setting: Academic rheumatology clinic/department, health spa Single Site	Total n = 60 Mean Age: 70.5 Arm 1, Mean Age: 72.45±7.14 BMI: 26.53±4 Arm 2, Mean Age: 69.33±7.63 BMI: 27.52±3 Female: 50% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: bilateral 100% Subtype: NR Diagnosis: ACR Analgesic Use: Yes, Patients in both groups were advised to continue their established pharmacological and non-pharmacological treatments, with the exception of analgesic drugs (500 mg acetaminophen tablets) and NSAIDs (150 mg Diclofenac tablets, 20 mg Piroxicam tablets, 750 mg Naproxen tablets, 200 mg Aceclofenac), which were to be consumed as required and noted daily in a diary.	Diagnosis of osteoarthritis of the knee Duration of Symptoms: >+3 months Minimum Age: 50 Maximum Age:75 ACR: NA VAS: >30mm K-L: 1-3	Concomitant medical problems that prevent participation Injected hyaluronic acid in the past or during the past 6 months month(s) Injected corticosteroids in the prior 3 months month(s) Physical Therapy or Rehab or exercise in the previous thermal treatments in the previous 6 months month(s) Severe comorbidity of the heart, lungs, liver, cerebrum or kidney, varices, systemic blood disease, neoplasm Acute illness Type 1 diabetes Pregnancy or nursing Arthroscopy with or without joint lavage in the previous 6 months, chondroprotective agents in the previous 6 months	Arm 1: Control n = 30 Duration: NA Arm 2: Balneotherapy n = 30 Dose: 20 minutes per treatment Frequency: 12 treatments per 2 weeks Duration: 2 weeks	<u>Lequesne index:</u> Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -7.50 95% CI: (-9.57, -5.43) <u>SF-36 mental component:</u> Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -17.00 95% CI: (-25.14, -8.86) <u>SF-36 physical component:</u> Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -32.60 95% CI: (-49.62, -15.58) <u>VAS pain:</u> Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -42.50 95% CI: (-53.67, -31.33) <u>WOMAC total function score:</u> Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -37.47 95% CI: (-46.61, -28.33) <u>WOMAC total pain score:</u> Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -25.70 95% CI: (-34.06, -17.34)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Fioravanti, 2015[75] Study design: RCT Trial name: None Study Location: Italy Health care setting: Spa resort Single Site	Total n = 103 Age Range: 40-80 Arm 1, Mean Age: 69.66 (11.1) BMI: 28.01 (4.18) Arm 2, Mean Age: 68.49 (9.01) BMI: 28.58 (4.01) Female: 72 Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: bilateral 100% Subtype: NR Diagnosis: K-L: 1-3, ACR Analgesic Use: Yes, Allowed but washout of concomitant acetaminophen or NSAIDs was required for an entire week before randomization and 24 h before every assessment.	Diagnosis of osteoarthritis of the knee Duration of Symptoms: 6 Minimum Age: 40 Maximum Age:79 VAS: >=30mm in last 3 months K-L: 1-3	Concomitant medical problems that prevent participation Injected hyaluronic acid in the past or during the past 3 month(s) Injected corticosteroids in the prior 3 month(s) Prior experience with the intervention of interest Symptomatic Slow Acting Drugs for OA (SYSADOA) in last 3 months	Arm 1: Usual care n = 50 Duration: 2 weeks Method of Blinding: Unblinded Arm 2: Mud-bath therapy n = 53 Dose: 35 minutes Frequency: 12 sessions Duration: 2 weeks Method of Blinding: Unblinded	<u>EQ-5D:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -0.10 95% CI: (NC, NC) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -0.24 95% CI: (NC, NC) <u>EQ-5D-VAS:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -22.09 95% CI: (-31.75, -12.43) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -14.35 95% CI: (-24.01, -4.69) <u>SF-12 mental component:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : 2.71 95% CI: (-6.95, 12.37) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : 1.92 95% CI: (-7.74, 11.58) <u>SF-12 physical component:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -11.85 95% CI: (-21.51, -2.19) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -12.46 95% CI: (-22.12, -2.80) <u>VAS:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -10.00 95% CI: (-21.31, 1.31) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -15.00 95% CI: (-25.63, -4.37)
Fioravanti, 2015[75] -Continued					<u>WOMAC function:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -5.50 95% CI: (-10.81, -0.19) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -10.00 95% CI: (-15.00, -5.00)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Fitzgerald, 2011[55] Study design: RCT Trial name: None Study Location: US Health care setting: NR Single Site	Total n = 183 Mean Age(SD): 64.5 (8.7) Arm 1, Mean Age: 65 (8.6) BMI: 30 (6.1) Arm 2, Mean Age: 63.8 (8.9) BMI: 29.8 (6.3) Female: 65% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: Tibiofemoral Diagnosis: K-L: >=2, ACR Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: 40 ACR: meet criteria for OAK K-L: >=2	Concomitant medical problems that prevent participation Prior surgery on one or both knees	Arm 1: Strength training; agility training; aerobic exercise n = 84 Placebo/Control Dose: N/A Frequency: Twice a week Duration: 6 weeks Method of Blinding: Unblinded Arm 2: Standard exercise + agility and perturbation training n = 75 Dose: N/A Frequency: Twice a week Duration: 6 weeks Method of Blinding: Unblinded	<u>WOMAC physical function score:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : 0.30 95% CI: (-3.59, 4.19) Follow-Up Time: 2 months : Comparator: Arm 2 vs Arm 1 , MD : -2.40 95% CI: (-5.87, 1.07) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -3.50 95% CI: (-7.32, 0.32) <u>WOMAC total:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : 0.40 95% CI: (-4.98, 5.78) Follow-Up Time: 2 months : Comparator: Arm 2 vs Arm 1 , MD : -3.00 95% CI: (-7.74, 1.74) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -4.50 95% CI: (-9.61, 0.61) <u>Get up and go test score (s):</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : 1.40 95% CI: (-0.13, 2.93) Follow-Up Time: 2 months : Comparator: Arm 2 vs Arm 1 , MD : -0.30 95% CI: (-0.94, 0.34) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -0.30 95% CI: (-0.75, 0.15) <u>Knee pain:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : 0.10 95% CI: (-0.89, 1.09) Follow-Up Time: 2 months : Comparator: Arm 2 vs Arm 1 , MD : -0.60 95% CI: (-1.38, 0.18) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -0.60 95% CI: (-1.45, 0.25)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Fitzgerald, 2016[67] Study design: RCT Trial name: None Study Location: US Health care setting: Hospital-outpatient, Academic physical therapy department, private hospital and military hospital Multiple Sites: 3	Total n = 300 Age Range: >=40 Arm 1, Mean Age: 58.3 (10.0) BMI: 30.1 (6.5) Arm 2, Mean Age: 58.4 (8.7) BMI: 31.4 (7.2) Arm 3, Mean Age: 58 (9.8) BMI: 31.1 (5.7) Arm 4, Mean Age: 58.5 (9.4) BMI: 31.7 (5.6) Female: 66% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: bilateral 60% Subtype: NR Diagnosis: ACR Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: >= 40 years ACR: diagnosis of OAK	Concomitant medical problems that prevent participation Prior surgery on one or both knees Prior TKA Prior total arthoplasty of any lower extremity joint Have back or leg pain in other areas besides your knee that affects your ability to perform physical activities History of neurological disorders that would affect lower extremity function (stroke, peripheral neuropathy, Parkinson's disease, multiple sclerosis)	Arm 1: Exercise therapy + no booster n = 75 Placebo/Usual care Dose: 45-60 min Frequency: 12 sessions Duration: 9 weeks Method of Blinding: Single-blind Arm 2: Exercise therapy + booster n = 76 Dose: 45-60 min Frequency: Participants receiving booster sessions completed eight sessions in the first 9 weeks, two booster sessions at 5 months, and one booster session at 8 and 11 months. Duration: 11 months Method of Blinding: Single-blind Co-Intervention: Booster Arm 3: Manual therapy + exercise therapy + no booster n = 75 Dose: 45-60 min Frequency: 9 sessions Duration: 12 weeks Method of Blinding: Single-blind Co-Intervention: Exercise therapy Arm 4: Manual therapy + exercise therapy + booster n = 74 Dose: 45-60 min Frequency: Participants receiving booster sessions completed eight sessions in the first 9 weeks, two booster sessions at 5 months, and one booster session at 8 and 11 months. Duration: 11 months Method of Blinding: Single-blind Co-Intervention: Exercise therapy + booster	<u>Knee pain rating:</u> Follow-Up Time: 1 year : Comparator: Arm 2 vs Arm 1 , MD : -0.60 95% CI: (-0.78, -0.42) Comparator: Arm 3 vs Arm 1 , MD : -0.20 95% CI: (-0.36, -0.04) Comparator: Arm 4 vs Arm 1 , MD : -0.70 95% CI: (-0.90, -0.50) Follow-Up Time: 9 week : Comparator: Arm 2 vs Arm 1 , MD : 0.60 95% CI: (0.42, 0.78) Comparator: Arm 3 vs Arm 1 , MD : 0.10 95% CI: (-0.06, 0.26) Comparator: Arm 4 vs Arm 1 , MD : 0.00 95% CI: (-0.20, 0.20) <u>TUG:</u> Follow-Up Time: 1 year : Comparator: Arm 2 vs Arm 1 , MD : -0.60 95% CI: (-0.78, -0.42) Comparator: Arm 3 vs Arm 1 , MD : -0.30 95% CI: (-0.46, -0.14) Comparator: Arm 4 vs Arm 1 , MD : 0.00 95% CI: (-0.21, 0.21) Follow-Up Time: 9 week : Comparator: Arm 2 vs Arm 1 , MD : -0.30 95% CI: (-0.48, -0.12) Comparator: Arm 3 vs Arm 1 , MD : -0.20 95% CI: (-0.36, -0.04) Comparator: Arm 4 vs Arm 1 , MD : -0.30 95% CI: (-0.51, -0.09) <u>WOMAC total:</u> Follow-Up Time: 1 year : Comparator: Arm 2 vs Arm 1 , MD : -3.40 95% CI: (-7.74, 0.94) Comparator: Arm 3 vs Arm 1 , MD : 2.00 95% CI: (-2.16, 6.16) Comparator: Arm 4 vs Arm 1 , MD : -5.80 95% CI: (-10.76, -0.84) Follow-Up Time: 9 week : Comparator: Arm 2 vs Arm 1 , MD : 6.60 95% CI: (2.26, 10.94) Comparator: Arm 3 vs Arm 1 , MD : -4.50 95% CI: (-8.66, -0.34) Comparator: Arm 4 vs Arm 1 , MD : -6.00 95% CI: (-10.96, -1.04)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Foroughi, 2011[52] Study design: RCT Trial name: None Study Location: Australia Health care setting: NR Single Site	Total n = 54 Age Range: >=40 Arm 1, Mean Age: 64 (8) BMI: 33.2 (8.1) Arm 2, Mean Age: 64 (7) BMI: 31.9 (5.2) Female: 100% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: Medial 74%, Lateral 26% Diagnosis: ACR Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: >40 ACR	Concomitant medical problems that prevent participation Surgery knee limb in prior 6 month(s) Injected hyaluronic acid in the past or during the past 6 month(s) Injected corticosteroids in the prior 6 month(s) Prior acute injury to the knee Secondary OA Men	Arm 1: Sham exercise n = 28 Placebo/Sham Dose: approx.40 minutes ( ) Frequency: Daily Duration: 6 months Method of Blinding: Single-blinded Arm 2: Progressive resistance training (PRT) n = 26 Dose: approx.60 minutes Frequency: Daily Duration: 6 months Method of Blinding: Single-blinded	<u>WOMAC function:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -7.49 95% CI: (-15.08, 0.10) <u>WOMAC pain:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -1.67 95% CI: (-3.71, 0.37) <u>WOMAC total:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -10.40 95% CI: (-20.56, -0.24)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Fransen, 2014[31] Study design: RCT Trial name: LEGS Study Location: Australia Health care setting: NR Site size: NR	Total n = 605 Age Range: 45-75 Arm 1, Mean Age: 60.6 (8.1) BMI: 29.1 (5.8) Arm 2, Mean Age: 61.2 (7.7) BMI: 28.4 (4.7) Arm 3, Mean Age: 60.7 (8.4) BMI: 28.8 (6.0) Arm 4, Mean Age: 59.5 (8.0) BMI: 29.6 (5.4) Female: 56% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: Medial 100% Diagnosis: K-L: <2 Analgesic Use: Yes, Not restricted	Diagnosis of osteoarthritis of the knee Duration of Symptoms: 6 months Pain >=4/10 Radiographs: Reduced joint space in medial tibial-femoral compartment but > 2mm	Concomitant medical problems that prevent participation Surgery knee limb in prior 6 month(s) Pending surgery Injected hyaluronic acid in the past or during the past 3 month(s) Injected corticosteroids in the prior 3 month(s) Rheumatoid arthritis Unstable diabetes Allergy to shellfish Bilateral knee replacement	Arm 1: Placebo n = 151 Placebo/Capsules Frequency: Once daily Duration: 2 years Method of Blinding: Double dummy Arm 2: Glucosamine n = 152 Dose: 1500 mg Frequency: Once daily Duration: 2 years Method of Blinding: Double dummy Arm 3: Glucosamine–chondroitin n = 151 Dose: 1500mg Glucosamine+ 800 mg Chondroitin Frequency: Once daily Duration: 2 years Method of Blinding: Double dummy Arm 4: Chondroitin n = 151 Dose: 800 mg Frequency: Once daily Duration: 2 years Method of Blinding: Double dummy	<u>SF-12 mental:</u> Follow-Up Time: 2 years : Comparator: Arm 2 vs Arm 1 , MD : -1.50 95% CI: (-3.99, 0.99) Comparator: Arm 3 vs Arm 1 , MD : -3.00 95% CI: (-5.19, -0.81) Comparator: Arm 4 vs Arm 1 , MD : -2.00 95% CI: (-4.45, 0.45) <u>SF-12 physical:</u> Follow-Up Time: 2 years : Comparator: Arm 2 vs Arm 1 , MD : 0.30 95% CI: (-2.04, 2.64) Comparator: Arm 3 vs Arm 1 , MD : 1.60 95% CI: (-0.83, 4.03) Comparator: Arm 4 vs Arm 1 , MD : 0.10 95% CI: (-2.27, 2.47) <u>WOMAC function:</u> Follow-Up Time: 2 years : Comparator: Arm 2 vs Arm 1 , MD : 0.00 95% CI: (-3.23, 3.23) Comparator: Arm 3 vs Arm 1 , MD : 0.00 95% CI: (-3.29, 3.29) Comparator: Arm 4 vs Arm 1 , MD : -0.40 95% CI: (-3.62, 2.82) <u>WOMAC pain:</u> Follow-Up Time: 2 years : Comparator: Arm 2 vs Arm 1 , MD : -0.10 95% CI: (-0.98, 0.78) Comparator: Arm 3 vs Arm 1 , MD : 0.10 95% CI: (-0.79, 0.99) Comparator: Arm 4 vs Arm 1 , MD : -0.20 95% CI: (-1.08, 0.68) <u>Pain:</u> Follow-Up Time: 2 years : Comparator: Arm 2 vs Arm 1 , MD : -0.17 95% CI: (-0.80, 0.46) Comparator: Arm 3 vs Arm 1 , MD : -0.45 95% CI: (-1.09, 0.19) Comparator: Arm 4 vs Arm 1 , MD : -0.27 95% CI: (-0.92, 0.38)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Ghroubi, 2008[123] Study design: RCT Trial name: None Study Location: Tunisia Health care setting: Physical therapy outpatient clinic Single Site	Total n = 56 Mean Age: 41 Arm 1, Mean Age: 42.4(9.8) BMI: 39.2 (3.7) Arm 2, Mean Age: 39.8(13.1) BMI: 37.1(5.7) Arm 3, Mean Age: 41.4(3.9) BMI: 37.45(3.68) Arm 4, Mean Age: 41.5(11.7) BMI: 38.74(6.15) Female: NR Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: K-L: mean 2.25, Mild to moderate Analgesic Use: Yes, Patients who changed their medication use during the study were excluded.	Diagnosis of osteoarthritis of the knee Minimum Age: 18 BMI>=35 or 30-35 with at least one chronic health risk factor Pain in the knee several days per week and having functional difficulties due to the OA, such as walking>1km, climbing stairs, housework, doing errands, lifting heavy load K-L: I=III	Prior surgery on one or both knees Prior acute injury to the knee An orthopedic problem that would prevent walking on a treadmill Treatment for another form of arthritis Contraindication to exercising Precursors to CVD or prior recent MI Serious psychiatric disorders	Arm 1: Control n = 14 Placebo/No diet or exercise Dose: NA Frequency: NA Duration: 2 months Arm 2: Land-based exercise n = 13 Dose: 60 minutes aerobic and strength training per session Frequency: 3 sessions per week Duration: 2 months Arm 3: Diet and exercise n = 15 Dose: 60 minutes per session Frequency: 3 sessions per week Duration: 2 months Arm 4: Diet only n = 14 Dose: NA Frequency: NA Duration: 2 months	<u>6 min walk:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -39.00 95% CI: (-46.47, -31.53) Comparator: Arm 3 vs Arm 1 , MD : -53.00 95% CI: (-59.33, -46.67) Comparator: Arm 4 vs Arm 1 , MD : 2.00 95% CI: (-6.51, 10.51) <u>Lequesne Index:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.41 95% CI: (-3.52, -1.30) Comparator: Arm 3 vs Arm 1 , MD : -3.73 95% CI: (-4.65, -2.81) Comparator: Arm 4 vs Arm 1 , MD : -2.23 95% CI: (-3.30, -1.16) <u>VAS:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.90 95% CI: (-4.52, -1.28) Comparator: Arm 3 vs Arm 1 , MD : -4.56 95% CI: (-5.82, -3.30) Comparator: Arm 4 vs Arm 1 , MD : -2.10 95% CI: (-3.32, -0.88) <u>WOMAC function:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -3.09 95% CI: (-4.46, -1.72) Comparator: Arm 3 vs Arm 1 , MD : -4.01 95% CI: (-5.56, -2.46) Comparator: Arm 4 vs Arm 1 , MD : -2.34 95% CI: (-3.71, -0.97) <u>Number with significant improvement in WOMAC:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , RR : 0.23 95% CI: (0.02, 2.23) Comparator: Arm 3 vs Arm 1 , RR : 0.16 95% CI: (0.02, 1.39) Comparator: Arm 4 vs Arm 1 , RR : 0.33 95% CI: (0.03, 3.43)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Gormeli, 2015[24] Study design: RCT Trial name: None Study Location: Turkey Health care setting: NR Site size: NR	Total n = 182 Age Range: 53.5 Arm 1, Mean Age: 52.8 (12.8) BMI: 29.5 (3.2) Arm 2, Mean Age: 53.8 (13.4) BMI: 28.4 (4.4) Arm 3, Mean Age: 53.7 (13.1) BMI: 28.7 (4.8) Arm 4, Mean Age: 53.5 (14) BMI: 29.7 (3.7) Female: 55.6% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: Tibiofemoral 100% Diagnosis: K-L: 1-4 Analgesic Use: Yes, Paracetamol was prescribed for discomfort.	Diagnosis of osteoarthritis of the knee Duration of Symptoms: > 4 months K-L: 1-4	Surgery knee limb in prior month(s) Systemic disorders (diabetes, rheumatic diseases, severe cardiovascular diseases, haematological diseases, infections) Generalized OA, Undergoing anticoagulant or antiaggregant therapy Use of NSAIDs in the 5 days before injection Hemoglobin values < 11 g/dL and platelet values < 150,000/mm3	Arm 1: Control n = 40 Frequency: One time treatment Arm 2: PRP1 n = 44 Frequency: One time treatment Arm 3: PRP3 n = 39 Frequency: One time treatment Arm 4: HA n = 39 Frequency: One time treatment	<u>EQ-VAS:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : 14.00 95% CI: (11.56, 16.44) Comparator: Arm 3 vs Arm 1 , MD : 23.40 95% CI: (19.66, 27.14) Comparator: Arm 4 vs Arm 1 , MD : 12.80 95% CI: (10.04, 15.56) <u>EuroQol-VAS:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -14.00 95% CI: (-16.44, -11.56) Comparator: Arm 3 vs Arm 1 , MD : -23.40 95% CI: (-27.14, -19.66) Comparator: Arm 4 vs Arm 1 , MD : -12.80 95% CI: (-15.56, -10.04)
Gschiel, 2010[86] Study design: RCT Trial name: None Study Location: Germany Health care setting: Academic pain clinic Single Site	Total n = 45 Mean Age: 58 Arm 1, Mean Age: 57.7(3.5) BMI: 29.6 Arm 2, Mean Age: 58.4(2.4) BMI: 27 Female: 75% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: NR Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: 18 Maximum Age:79 Body weight 50-100kg Chronic pain (at least 4/11 NRS) radiologically verified diagnosis: NR	Concomitant medical problems that prevent participation Prior experience with the intervention of interest CVD Permanent pacemaker Neurologic disease Inflammatory joint disease Cancer	Arm 1: Placebo n = 20 Dose: 30 minutes per treatment session Frequency: two sessions per day Duration: 3 weeks Arm 2: TENS n = 25 Dose: 30 minutes per treatment session Frequency: two sessions per day Duration: 3 weeks	<u>WOMAC Pain:</u> Follow-Up Time: 5 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.00 95% CI: (-2.85, 0.85) <u>WOMAC total:</u> Follow-Up Time: 5 weeks : Comparator: Arm 2 vs Arm 1 , MD : -4.20 95% CI: (-18.43, 10.03)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Hatef, 2014[105] Study design: RCT Trial name: None Study Location: Iran Health care setting: NR Site size: NR	Total n = 150 Arm 1, Mean Age: 48.6 (10) at end line Arm 2, Mean Age: 48.21 (12) at end line Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: Medial 100%, Tibiofemoral 100% Diagnosis: Mild-to-moderate, ACR Analgesic Use: Yes, Unrestricted? Not detailed	Diagnosis of osteoarthritis of the knee Duration of Symptoms: Pain on a daily basis for at least 1 month during the previous 3 months K-L: >2 Clinical diagnosis: Medial femoro-tibial OA	Concomitant medical problems that prevent participation Injected corticosteroids in the prior 1 month(s) Knee joint lavage within the previous 3 months Tibial osteotomy within the previous 5 years Drug treatment for OA within the previous week Greater or similar reduction in lateral than medial femoro-tibial joint space width Secondary knee or hip OA	Arm 1: Neutral insoles n = 75 Placebo/Sham Duration: 2 months Method of Blinding: Double-blinded Arm 2: Lateral wedged insoles n = 75 Duration: 2 months Method of Blinding: Double-blinded	<u>VAS:</u> Follow-Up Time: 2 months : Comparator: Arm 2 vs Arm 1 , MD : -23.05 95% CI: (-28.34, -17.76) <u>VAS - number pain mild (21-40):</u> Follow-Up Time: 2 months : Comparator: Arm 2 vs Arm 1 , RR : 0.13 95% CI: (0.05, 0.36) <u>VAS - number pain none to scant (0-20):</u> Follow-Up Time: 2 months : Comparator: Arm 2 vs Arm 1 , RR : 0.23 95% CI: (0.03, 2.03)
Henriksen, 2014[56] Study design: RCT Trial name: None Study Location: Denmark Health care setting: Hospital-outpatient Single Site	Total n = 60 Age Range: >=40 Arm 1, Mean Age: 62.3 (7.1) BMI: 28.2 (4.6) Arm 2, Mean Age: 65 (8.9) BMI: 28.9 (4.1) Female: 80% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: Tibiofemoral 100% Diagnosis: Diagnosis of tibiofemoral OA confirmed by radiography Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: >=40 Body mass index between 20 and 35 clinical diagnosis of tibiofemoral OA confirmed by radiography	Concomitant medical problems that prevent participation Physical Therapy or Rehab or exercise in the previous 3 month(s) Systemic inflammatory and autoimmune disease Significant cardiovascular, neurologic, or psychiatric disease, cervical or lumbar nerve root compression syndromes, and wide spread or regional pain syndromes (e.g., fibromyalgia) Lower extremity joint replacement	Arm 1: Control n = 23 Placebo/Control Duration: 12 weeks Arm 2: Exercise therapy n = 25 Dose: 1 hour Frequency: 3 times a week Duration: 12 weeks	<u>KOOS function:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.80 95% CI: (-9.02, 3.42) <u>KOOS pain:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -6.80 95% CI: (-12.18, -1.42) <u>KOOS quality of life:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -6.10 95% CI: (-14.16, 1.96)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Herrero-Beaumont, 2016[32] Study design: RCT Trial name: None Study Location: Spain Health care setting: Academic orthopedic surgery clinic/department, Academic rheumatology clinic/department Multiple Sites: 9	Total n = 158 Arm 1, Mean Age: 65 (8) BMI: 28.5 (3.4) Arm 2, Mean Age: 67 (8) BMI: 27.9 (3.2) Female: 85% T, 81% C Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: 2&3, ACR Analgesic Use: Yes, Another confounding factor is the analgesic effect due to pain killer rescue medication allowed in all OA clinical trials.	Diagnosis of osteoarthritis of the knee Were required to complain of moderate-severe pain as defined by a score of 40 80 mm in Visual Analog Scale (VAS) ACR: primary symptomatic OAK K-L: 2&3	Concomitant medical problems that prevent participation . Exclusion criteria included obesity [body mass index (BMI) _ 35 kg/m2], concurrent arthritic conditions, or any coexisting disease that could preclude successful completion of the stud	Arm 1: Chondroitin sulfate + glucosamine sulfate n = 80 Placebo/Placebo Dose: 1200mg CS + 1500mg GS Frequency: Once daily Duration: 6 months Method of Blinding: Double blind Arm 2: Placebo n = 78 Frequency: Once daily Duration: 6 months Method of Blinding: Double blind	<u>VAS pain:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : 8.70 95% CI: (7.95, 9.45) <u>WOMAC function:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : 5.30 95% CI: (4.68, 5.92) <u>WOMAC pain:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : 6.90 95% CI: (6.21, 7.59) <u>WOMAC total:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : 5.90 95% CI: (5.28, 6.52)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Hochberg, 2008[134] Study design: RCT Trial name: GAIT Study Location: US Health care setting: Academic rheumatology clinic/department Multiple Sites: 16	Total n = 1583 Total # of knees = NR Age Range: NR Arm 1, Mean Age: 58(10) BMI: 31.9(7.3) Arm 2, Mean Age: 59(10) BMI: 31.8(6.8) Arm 3, Mean Age: 58(10) BMI: 32.0(7.6) Arm 4, Mean Age: 59(11) BMI: 31.5(6.6) Arm 5, Mean Age: 59(11) BMI: 31.5(7.1) Female: 64% Racial/Ethnic Distribution: African American 14%, Asian NR, Caucasian 78%, NR Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: K-L: 2&3, WOMAC pain scores 125-400 out of 500, Functional class I, II, or III Analgesic Use: Yes, Patients were allowed to take up to 4000 mg of acetaminophen (Tylenol, McNeil) daily, except during the 24 hours before a clinical evaluation for joint pain. Otheranalgesics, including narcotics and NSAIDs, were not permitted.	Diagnosis of osteoarthritis of the knee Minimum Age: 40 Ambulatory Knee pain for at least six months and on the majority of days during the preceding month K-L: 2&3 ACR: 1, II, or III WOMAC: 125-400mm	Concomitant medical problems that prevent participation Prior surgery on one or both knees Prior acute injury to the knee Concurrent medical or arthritic conditions that could confound evaluation of the index joint Concurrent use of analgesics other than acetominophen, including NSAIDs or narcotics Predominant patellofemoral disease A history of clinically significant trauma or surgery to the index knee	Arm 1: Placebo n = 313 Dose: NA (not applicable) Frequency: 3 times a day Duration: 24 weeks Method of Blinding: NR Arm 2: Glucosamine n = 317 Dose: 500mg Frequency: three times a day Duration: 24 weeks Method of Blinding: NA Arm 3: Chondroitin sulfate n = 318 Dose: 400 mg Frequency: three times a day Duration: 24 weeks Method of Blinding: NA Arm 4: Glucosamine+chondroitin sulfate n = 317 Dose: 500 mg G + 400 mg CS Frequency: three times a day Duration: 24 weeks Method of Blinding: NA Arm 5: Celecoxib n = 318 Dose: 200 mg Frequency: once a day Duration: 24 weeks Method of Blinding: NA	<u>WOMAC pain (% with 20% or better improvement in pain:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , RR : 0.94 95% CI: (0.83, 1.06) Comparator: Arm 3 vs Arm 1 , RR : 0.92 95% CI: (0.81, 1.04) Comparator: Arm 4 vs Arm 1 , RR : 0.90 95% CI: (0.80, 1.02) Comparator: Arm 5 vs Arm 1 , RR : 0.86 95% CI: (0.76, 0.96)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Hochberg, 2015[29] Study design: RCT Trial name: MOVES Study Location: France, Germany, Poland and Spain Health care setting: NR Multiple Sites: 42	Total n = 606 Age Range: >=40 Arm 1, Mean Age: 63.2 (9.0) BMI: 30.9 (18.0) Arm 2, Mean Age: 62.2 (8.8) BMI: 31.1 (5.8) Female: 83.9% Racial/Ethnic Distribution: Caucasian 98.7%, 1.3% Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: 2&3, ACR Analgesic Use: Yes, Up to 3 g/day of acetaminophen except during the 48 h before clinical evaluation	Diagnosis of osteoarthritis of the knee: ACR Duration of Symptoms: 1 month Minimum Age: 40 Otherwise Healthy Able to sign Consent No clinical or significant laboratory abnormalities Negative pregnancy test and use of birth control Not participating in another clinical trial Agree to attend all study-related visits K-L: 2&3 WOMAC: >301	Concomitant medical problems that prevent participation Prior surgery on one or both knees Surgery knee limb in prior 6 month(s) Pending surgery Concomitant or prior use of other meds Known allergy to chondroitin, glucosamine, celecoxib, sulphonamides, aspirin, lactose, NSAIDs, Allergy to shellfish Intolerance to acetaminophen History of systemic diseases (heart attack or stroke, DM, hypertension, chronic liver/kidney diseases, infections); history of psychiatric disorders, alcohol/drug abuse Active malignancy or history of a malignancy within the past 5 years Concurrent arthritic disease, pain in other parts of the body, fibromyalgia	Arm 1: Celecoxib n = 282 Dose: 200mg Frequency: Once daily Duration: 6 months Method of Blinding: Matching capsules Arm 2: Glucosamine-chondroitin n = 286 Dose: 500 mg Glucosamine+400 mg Chondroitin Frequency: Three time daily Duration: 6 months	<u>% clinically significant on WOMAC pain:</u> Follow-Up Time: 180 days : Comparator: Arm 2 vs Arm 1 , RR : 1.00 95% CI: (0.85, 1.17) <u>EuroQol-5D mobility:</u> Follow-Up Time: 180 days : Comparator: Arm 2 vs Arm 1 , MD : 0.00 95% CI: (-0.00, 0.00) <u>EuroQol-5D pain/discomfort:</u> Follow-Up Time: 180 days : Comparator: Arm 2 vs Arm 1 , MD : 0.10 95% CI: (0.10, 0.10) <u>WOMAC function:</u> Follow-Up Time: 180 days : Comparator: Arm 2 vs Arm 1 , MD : 21.20 95% CI: (-44.99, 87.39) Follow-Up Time: 60 days : Comparator: Arm 2 vs Arm 1 , MD : 71.50 95% CI: (NC, NC) <u>WOMAC pain:</u> Follow-Up Time: 180 days : Comparator: Arm 2 vs Arm 1 , MD : 1.10 95% CI: (-19.76, 21.96) Follow-Up Time: 60 days : Comparator: Arm 2 vs Arm 1 , MD : 25.00 95% CI: (5.05, 44.95) <u>Clinically significant on WOMAC function:</u> Follow-Up Time: 180 days : Comparator: Arm 2 vs Arm 1 , RR : 1.02 95% CI: (0.86, 1.21)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Hsieh, 2012[78] Study design: RCT Trial name: None Study Location: Taiwan Health care setting: NR Single Site	Total n = 72 Mean Age(SD): Mean: 60.3 (10.4) Arm 1, Mean Age: 61.3 (12) BMI: 26 (4.5) Arm 2, Mean Age: 61.1 (9.4) BMI: 26.4 (5.0) Female: 86% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: II+ in both knees, ACT Analgesic Use: NR	Diagnosis of osteoarthritis of the knee K-L: II+ in both knees ACR	Concomitant medical problems that prevent participation Surgery knee limb in prior Ever month(s) Pregnant or planning to become pregnant, and those who had a self-reported history of malignancy, vertigo, or stroke.	Arm 1: Sham monochromatic infrared energy (MIRE) n = 35 Placebo/Sham Dose: 40 minutes Frequency: 3 times a week Duration: 2 weeks Method of Blinding: Double-blind Arm 2: Monochromatic infrared energy (MIRE) n = 37 Dose: 40 minutes Frequency: 3 times a week Duration: 2 weeks Method of Blinding: Double-blind	<u>KOOS pain:</u> Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.70 95% CI: (-7.74, 4.34) <u>KOOS quality of life:</u> Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.10 95% CI: (-6.39, 6.59) <u>OAQOL:</u> Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.30 95% CI: (-2.70, 2.10) <u>WHOQOL-BREF physical:</u> Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.80 95% CI: (-8.48, 4.88) <u>WHOQOL-BREF psychological:</u> Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -4.40 95% CI: (-11.19, 2.39)
Imoto, 2012[48] Study design: RCT Trial name: None Study Location: Brazil Health care setting: Academic rheumatology clinic/department Single Site	Arm 1, Mean Age: 58.78 (9.60) BMI: 30.00 (5.05) Arm 2, Mean Age: 61.50 (6.94) BMI: 29.72 (4.11) Female: 92% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: bilateral 26%, unilateral 74% Subtype: NR Diagnosis: K-L: 92% Grade II, 5% Grade III, 3% Grade IV, NRS pain 7.2 Analgesic Use: Yes, Patients were allowed to continue their medications, but paracetamol, diacerein, and chloroquin were used	Diagnosis of osteoarthritis of the knee Minimum Age: 50 Maximum Age:75 Knee pain Less than 30 minutes morning stiffness and crepitation in active movement and osteophytes ACR K-L: 2 or above in past 12 months	Physical therapy more than twice a week Inability to pedal a bike Unstable heart condition Fibromyalgia Prior knee arthroplasty	Arm 1: Control n = 50 Placebo/Educational manual and 2 phone calls Dose: NA Frequency: NA Duration: 8 weeks Method of Blinding: NR Arm 2: Land-based strength training n = 50 Dose: 30-40 minutes per session Frequency: two sessions per week Duration: 8 weeks Method of Blinding: NR Co-Intervention: Orientation manual	<u>Numerical Rating Scale for pain:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.47 95% CI: (-2.71, -0.23) <u>SF-36 functional capacity:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -7.83 95% CI: (-18.92, 3.26) <u>SF-36 pain:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.98 95% CI: (-13.94, 7.98) <u>SF-36 physical aspects:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -13.47 95% CI: (-33.97, 7.03) <u>TUG (s):</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.80 95% CI: (-2.97, -0.63)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Imoto, 2013[84] Study design: RCT Trial name: None Study Location: Brazil Health care setting: Hospital-outpatient Single Site	Total n = 100 Mean Age: 59.7 Arm 1, Mean Age: 58.8 (9.6) BMI: 30 (5) Arm 2, Mean Age: 60.6 (6.7) BMI: 30 (4) Female: 93% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: bilateral 72% (96% for NMES group) Subtype: NR Diagnosis: K-L: 93% grade II, 4% grade III, 3% grade IV Analgesic Use: Yes, Patients' continued medications during intervention but paracetamol, diacerein, and chloroquine were prescribed	Diagnosis of osteoarthritis of the knee Minimum Age: 50 Maximum Age:75 ACR: NA K-L: Grade 2 or more in the prior 12 months	Use of pacemaker, unstable cardiac status, Attendance in a physical activity program more than twice a week Inability to ride a stationary bike, or to walk Previous arthroplasty	Arm 1: Control group n = 50 Placebo/Educational materials Dose: NA Frequency: NA Duration: 8 weeks Method of Blinding: NR Arm 2: NMES n = 50 Dose: 40 minutes per session Frequency: NR Duration: 8 weeks Method of Blinding: NR Co-Intervention: Educational guide	<u>Lequesne Index:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.81 95% CI: (-4.53, -1.09) <u>NRS:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.44 95% CI: (-2.65, -0.23) <u>TUG (s):</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.45 95% CI: (-3.42, -1.48)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Inal, 2016[89] Study design: RCT Trial name: None Study Location: Turkey Health care setting: NR Site size: NR	Total n = 93 Arm 1, Mean Age: 64.6 (1.88) BMI: 33.6 (0.77) Arm 2, Mean Age: 64.4 (1.7) BMI: 34.2 (0.87) Arm 3, Mean Age: 64.1 (0.99) BMI: 31.7 (0.92) Female: 100% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: I1-4, ACR Analgesic Use: No	Diagnosis of osteoarthritis of the knee ACR: symptomatic knee OA	Concomitant medical problems that prevent participation Prior surgery on one or both knees Concomitant or prior use of other meds Injected hyaluronic acid in the past or during the past 3 month(s) Injected corticosteroids in the prior 3 month(s) Prior acute injury to the knee Had received TENS in the previous six months and had cardiac pace-maker, Complaints linked to lower extremities such as radiculopathy or pain on ankle Used non-steroidal anti-inflammatory drugs and chondroprotective agents in the last month Uncontrolled co-morbid chronic disease such as diabetes mellitus and hypertension, a poor general health status, definite/suspected pregnancy, dementia or cognitive impairment, neurological disorders such as multiple sclerosis, Parkinson's and Alzheimer's diseases, major trauma in last 6 months	Arm 1: Sham TENS + physical therapy n = 30 Placebo/Sham Dose: 20 minutes Frequency: 5 times per week Duration: 2 weeks (TENS) / 4 weeks (home exercise) Method of Blinding: Double blind Arm 2: Low frequency TENS + physical therapy n = 30 Dose: 20 minutes Frequency: 5 times per week Duration: 2 weeks (TENS) / 4 weeks (home exercise) Method of Blinding: Double blind Arm 3: High frequency TENS + physical therapy n = 30 Dose: 20 minutes Frequency: 5 times per week Duration: 2 weeks (TENS) / 4 weeks (home exercise) Method of Blinding: Double blind	<u>VAS pain in motion:</u> Follow-Up Time: 6 weeks : Comparator: Arm 3 vs Arm 1 , MD : 0.02 95% CI: (-1.82, 1.86) <u>VAS pain in rest:</u> Follow-Up Time: 6 weeks : Comparator: Arm 3 vs Arm 1 , MD : 0.26 95% CI: (-1.62, 2.14) <u>WOMAC function:</u> Follow-Up Time: 6 weeks : Comparator: Arm 3 vs Arm 1 , MD : -0.95 95% CI: (-8.46, 6.55) <u>WOMAC pain:</u> Follow-Up Time: 6 weeks : Comparator: Arm 3 vs Arm 1 , MD : -0.62 95% CI: (-3.01, 1.78) <u>WOMAC total:</u> Follow-Up Time: 6 weeks : Comparator: Arm 3 vs Arm 1 , MD : -1.73 95% CI: (-10.83, 7.37)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Inoshi, 2016[128] Study design: Single arm trial Trial name: Healthy weight for life Study Location: Australia Health care setting: internet and phone-based program Multiple Sites: NR (internet-based)	Total n = 1383 Mean Age(SD): Mean age 64.0(8.7) Arm 1, Mean Age: 64(8.7) BMI: 34.4(5.2) Female: 70.9% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: K-L: not specified, Mean KOOS pain 56.3(6.8) Analgesic Use: NR	Diagnosis of osteoarthritis of the knee BMI>28 Referral to orthopedist for KR Enrollment in OAHWFL program Radiographic or arthroscopy: NR	Exclusion : NR	Arm 1: Weight loss and exercise n = 1383 Dose: NA Frequency: NA Duration: 18 weeks	<u>KOOS function:</u> Follow-Up Time: 18 weeks : Comparator: >10% weight change (post-pre) , MD : 17.40 95% CI: (15.9, 18.9) Comparator: 7.6-10% weight change (post-pre) , MD : 13.60 95% CI: (11.9, 15.3) Comparator: 5.1-7.5% weight change (post-pre) , MD : 12.00 95% CI: (10.2, 13.8) Comparator: 2.5-5% weight change (post-pre) , MD : 8.90 95% CI: (7.0, 10.8) Comparator: <2.5% weight change (post-pre) , MD : 7.80 95% CI: (4.8, 10.8) <u>KOOS pain:</u> Follow-Up Time: 18 weeks : Comparator: >10% weight change (post-pre) , MD : 16.70 95% CI: (15.2, 18.2) Comparator: 7.6-10% weight change (post-pre) , MD : 13.30 95% CI: (11.6, 15.0) Comparator: 5.1-7.5% weight change (post-pre) , MD : 12.00 95% CI: (10.2, 13.8) Comparator: 2.5-5% weight change (post-pre) , MD : 9.90 95% CI: (7.7, 12.1) Comparator: <2.5% weight change (post-pre) , MD : 6.10 95% CI: (3.2, 9.0)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Jones, 2012[115] Study design: RCT Trial name: None Study Location: Brazil Health care setting: Academic rheumatology clinic/department Single Site	Total n = 64 Arm 1, Mean Age: 62.56 (5.88) BMI: 29.54 (3.42) Arm 2, Mean Age: 61.75 (5.92) BMI: 29.01 (2.83) Living Situation: Community Dwelling Diagnosis: VAS 5.56/10, WOMAC 51.0/96 Analgesic Use: Yes, Stable use of analgesics	Diagnosis of osteoarthritis of the knee Stable doses of anti-inflammatory drugs No regular physical exercise in the month before the study ACR: NA VAS: 3-7/10	Injected hyaluronic acid in the past or during the past 3 months month(s) Injected corticosteroids in the prior 3 months month(s) Physical Therapy or Rehab or exercise in the previous physical therapy in the previous 6 months or rehab in the previous 3 months month(s) Prior experience with the intervention of interest Symptomatic heart disease Symptomatic disease of the lower limbs (other than knee osteoarthritis) or upper limb that would secure the cane Symptomatic lung disease; severe systemic disease; severe psychiatric illness Regular physical exercise; (three or more times per week for at least 3 months) Inability to walk; geographic inaccessibility	Arm 1: Control n = 32 Duration: 2 months Arm 2: Braces or Canes n = 32 Dose: NA Frequency: NA Duration: 2 months Co-Intervention: usual therapy	<u>6 min walk with cane (m):</u> Follow-Up Time: 60 days : Comparator: Arm 2 vs Arm 1 , MD : 83.28 95% CI: (62.38, 104.18) <u>6 min walk without cane (m):</u> Follow-Up Time: 60 days : Comparator: Arm 2 vs Arm 1 , MD : -6.50 95% CI: (-24.86, 11.86) <u>Lequesne:</u> Follow-Up Time: 60 days : Comparator: Arm 2 vs Arm 1 , MD : -2.53 95% CI: (-4.34, -0.72) <u>SF-36 bodily pain:</u> Follow-Up Time: 60 days : Comparator: Arm 2 vs Arm 1 , MD : -14.16 95% CI: (-24.30, -4.02) <u>SF-36 physical function:</u> Follow-Up Time: 60 days : Comparator: Arm 2 vs Arm 1 , MD : -9.06 95% CI: (-17.81, -0.31) <u>SF-36 role physical:</u> Follow-Up Time: 60 days : Comparator: Arm 2 vs Arm 1 , MD : -16.75 95% CI: (-31.69, -1.81) <u>VAS pain:</u> Follow-Up Time: 60 days : Comparator: Arm 2 vs Arm 1 , MD : -2.11 95% CI: (-2.83, -1.39) <u>WOMAC total:</u> Follow-Up Time: 60 days : Comparator: Arm 2 vs Arm 1 , MD : -1.06 95% CI: (-8.87, 6.75)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Jorge, 2015[49] Study design: RCT Trial name: None Study Location: Brazil Health care setting: NR Site size: NR	Total n = 60 Age Range: 40-70 Arm 1, Mean Age: 59.9 (7.5) BMI: 31.4 (4.42) Arm 2, Mean Age: 61.7 (6.4) BMI: 30.6 (5.75) Female: 100 Racial/Ethnic Distribution: Caucasian 69% T, 71% C Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: ACR Analgesic Use: Yes, All subjects were instructed to take 750 mg of acetaminophen every eight hours when experiencing pain. When pain exceeded a 7 on the visual analog scale, the subject could take 50 mg of diclofenac every eight hours. Both groups received a chart to record the doses of drugs taken during the study period for the purposes of analysis.	Diagnosis of osteoarthritis of the knee Minimum Age: >=40 Maximum Age:69 Pain at rest between 3 and 8 out of 10 on the visual analog scale for one or both knees ACR: meets criteria	Concomitant medical problems that prevent participation Injected hyaluronic acid in the past or during the past 3 month(s) Injected corticosteroids in the prior 3 month(s) Inflammatory conditions or any medical condition that prevented physical activity Travel plans for the subsequent 12 weeks Regular physical activity at the time	Arm 1: Waitlist n = 31 Placebo/Waitlist Duration: 12 weeks Method of Blinding: Single-blind Arm 2: Progressive resistance exercise n = 29 Dose: 2 set of 8 reps w/ 1 min rest period between sets Frequency: Twice a week Duration: 12 weeks Method of Blinding: Single-blind	<u>6MWT:</u> Follow-Up Time: 45 days : Comparator: Arm 2 vs Arm 1 , MD : -15.60 95% CI: (-45.14, 13.94) Follow-Up Time: 90 days : Comparator: Arm 2 vs Arm 1 , MD : -26.40 95% CI: (-55.73, 2.93) <u>SF-36 mental health:</u> Follow-Up Time: 45 days : Comparator: Arm 2 vs Arm 1 , MD : -16.10 95% CI: (-26.66, -5.54) Follow-Up Time: 90 days : Comparator: Arm 2 vs Arm 1 , MD : -16.90 95% CI: (-27.00, -6.80) <u>SF-36 physical health:</u> Follow-Up Time: 45 days : Comparator: Arm 2 vs Arm 1 , MD : -8.80 95% CI: (-17.26, -0.34) Follow-Up Time: 90 days : Comparator: Arm 2 vs Arm 1 , MD : -19.00 95% CI: (-28.93, -9.07) <u>VAS pain:</u> Follow-Up Time: 45 days : Comparator: Arm 2 vs Arm 1 , MD : -1.10 95% CI: (-2.02, -0.18) Follow-Up Time: 90 days : Comparator: Arm 2 vs Arm 1 , MD : -2.30 95% CI: (-3.55, -1.05) <u>WOMAC function:</u> Follow-Up Time: 45 days : Comparator: Arm 2 vs Arm 1 , MD : -4.00 95% CI: (-9.04, 1.04) Follow-Up Time: 90 days : Comparator: Arm 2 vs Arm 1 , MD : -9.40 95% CI: (-15.17, -3.63)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Jorge, 2015[49] - Continued					<u>WOMAC pain:</u> Follow-Up Time: 45 days : Comparator: Arm 2 vs Arm 1 , MD : -3.40 95% CI: (-5.10, -1.70) Follow-Up Time: 90 days : Comparator: Arm 2 vs Arm 1 , MD : -4.60 95% CI: (-6.50, -2.70) <u>WOMAC total:</u> Follow-Up Time: 45 days : Comparator: Arm 2 vs Arm 1 , MD : -8.20 95% CI: (-14.78, -1.62) Follow-Up Time: 90 days : Comparator: Arm 2 vs Arm 1 , MD : -14.20 95% CI: (-22.03, -6.37)
Ju, 2015[57] Study design: RCT Trial name: None Study Location: Korea Health care setting: NR Site size: NR	Total n = 14 Age Range: NR Arm 1, Mean Age: 65.1 ± 2.9 BMI: Average weight: 60.6 ± 7.69 kg, average height 153.1 ± 4.5 cm and Arm 2, Mean Age: 65.7 ± 3.5 BMI: average weight of 64.7 ± 2.3 kg, height 152.4 ± 5.1 cm and an Female: 100% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: ACR Analgesic Use: NR	Minimum Age: 60	Exclusion : NR	Arm 1: Control n = 7 Duration: NR Arm 2: Agility-type exercise n = 7 Dose: 20 minutes (3 sets of 10 repetitions per exercise) per session Frequency: 3 sessions per week Duration: 8 weeks	<u>VAS pain:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -4.00 95% CI: (-5.32, -2.68)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Kahan, 2009[38] Study design: RCT Trial name: None Study Location: US, France, Belgium, Switzerland, Austria Health care setting: Hospital-outpatient Multiple Sites: 35	Total n = 622 Age Range: 45-80 Arm 1, Mean Age: 61.8(0.5) BMI: 28.8 Arm 2, Mean Age: 62.9(0.5) BMI: 28.5 Female: 68.5% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: Medial 100% Diagnosis: ACR Analgesic Use: Yes, Acetaminophen in 500-mg tablets (maximum dosage 4 gm/day); NSAIDs were allowed in cases of acute pain.	Diagnosis of osteoarthritis of the knee Duration of Symptoms: 3 months Minimum Age: 45 Maximum Age:79 ACR VAS: >= 30 mm JSW: >= 1 mm	Concomitant medical problems that prevent participation Prior surgery on one or both knees Concomitant or prior use of other meds Injected hyaluronic acid in the past or during the past 3 month(s) Injected corticosteroids in the prior 3 month(s) Prior acute injury to the knee K-L: 4 Isolated lateral tibiofemoral OA; isolated patellofemoral OA A history or the active presence of other rheumatic diseases that could be responsible for secondary OA A history of hip OA or hip surgery	Arm 1: Placebo n = 313 Placebo/Sachet Frequency: Once daily Arm 2: Chondroitins sulfate n = 309 Dose: 800 mg Frequency: Once daily	<u>VAS pain last 48 hours:</u> Follow-Up Time: 24 months : Comparator: Arm 2 vs Arm 1 , MD : 0.50 95% CI: (-2.27, 3.27) Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -4.00 95% CI: (-8.16, 0.16) <u>WOMAC pain score last 48 hours:</u> Follow-Up Time: 24 months : Comparator: Arm 2 vs Arm 1 , MD : -2.00 95% CI: (-6.16, 2.16) Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -3.50 95% CI: (-7.66, 0.66) <u>Responder: reduction in pain score of at least 40% WOMAC:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , RR : 0.83 95% CI: (0.68, 1.02) <u>Responder: reduction in pain score of at least 40mm:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , RR : 0.68 95% CI: (0.51, 0.91) <u>Responder: reduction in pain score of at least 60mm:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , RR : 0.44 95% CI: (0.23, 0.85)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Kapci, 2015[81] Study design: RCT Trial name: None Study Location: Turkey Health care setting: NR Site size: NR	Total n = 90 Age Range: 40-65 Arm 1, Mean Age: 57.76 (7.15) BMI: 30.91 (4.33) Arm 2, Mean Age: 56.13 (6.61) BMI: 32.31 (5.23) Arm 3, Mean Age: 54.63 (6.53) BMI: 31.15 (4.68) Female: 83% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: bilateral 100% Subtype: NR Diagnosis: K-L: 2&3 Analgesic Use: NR		Concomitant medical problems that prevent participation Prior surgery on one or both knees Injected hyaluronic acid in the past or during the past 6 month(s) Injected corticosteroids in the prior 6 month(s) Secondary knee OA; active synovitis; symptomatic hip, foot, and ankle disease; neurologic deficits in a lower extremity; recent knee trauma Application of physical treatment to the knee in the last 3 months	Arm 1: Sham ultrasound n = 30 Placebo/Sham Dose: 5 min Frequency: 5 days a week Duration: 2 weeks US / 8 weeks exercise Method of Blinding: Double blind Arm 2: Continuous ultrasound n = 30 Dose: 5 min Frequency: 5 days a week Duration: 2 weeks US / 8 weeks exercise Method of Blinding: Double blind Arm 3: Pulsed ultrasound n = 30 Dose: 5 min Frequency: 5 days a week Duration: 2 weeks US / 8 weeks exercise Method of Blinding: Double blind	<u>Lequesne index:</u> Follow-Up Time: 2 months : Comparator: Arm 2 vs Arm 1 , MD : -2.35 95% CI: (-4.11, -0.59) Comparator: Arm 3 vs Arm 1 , MD : -2.65 95% CI: (-4.27, -1.03) Follow-Up Time: 4 months : Comparator: Arm 2 vs Arm 1 , MD : -6.28 95% CI: (-8.31, -4.25) Comparator: Arm 3 vs Arm 1 , MD : -5.71 95% CI: (-7.68, -3.74) <u>VAS pain:</u> Follow-Up Time: 2 months : Comparator: Arm 2 vs Arm 1 , MD : -1.33 95% CI: (-2.55, -0.11) Comparator: Arm 3 vs Arm 1 , MD : -1.56 95% CI: (-2.82, -0.30) Follow-Up Time: 4 months : Comparator: Arm 2 vs Arm 1 , MD : -3.30 95% CI: (-4.62, -1.98) Comparator: Arm 3 vs Arm 1 , MD : -3.37 95% CI: (-4.70, -2.04)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Knoop, 2013[61] Study design: RCT Trial name: None Study Location: Netherlands Health care setting: Physical therapy outpatient clinic Single Site	Total n = 159 Mean Age: 62 Arm 1, Mean Age: 61.8 _x0006_ (6.6) BMI: 28.3(4.5) Arm 2, Mean Age: 62.1(7.6) BMI: 28.8(4.8) Female: 66% intervention; 56% control Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: bilateral 75%, unilateral 25% Subtype: NR Diagnosis: K-L: 35% K-L: I; 28% K-L: II; 26% K-L: III; 12% K-L: IV Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: 40 Maximum Age:75 Ambulatory Self-reported or bio-assessed knee instability ACR: NA	Concomitant medical problems that prevent participation Pending surgery Other diagnosed forms of arthritis Severe knee pain (NRS>8) Inability to comprehend Dutch, be scheduled for therapy or provide consent	Arm 1: Land-based exercise n = 79 Dose: 60 minutes per session Frequency: 2 sessions per week plus home exercises 5 days per week Duration: 12 weeks Method of Blinding: NR Arm 2: Agility type training n = 80 Dose: 60 minutes per session Frequency: 2 sessions per week plus home exercises 5 days per week Duration: 12 weeks Method of Blinding: NR	<u>NRS:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.50 95% CI: (-1.16, 0.16) Follow-Up Time: 38 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.60 95% CI: (-1.37, 0.17) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.20 95% CI: (-0.83, 0.43) <u>TUG (s):</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.40 95% CI: (-0.16, 0.96) Follow-Up Time: 38 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.10 95% CI: (-0.47, 0.67) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.10 95% CI: (-0.63, 0.83) <u>WOMAC physical function:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.90 95% CI: (-5.53, 1.73) Follow-Up Time: 38 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.30 95% CI: (-4.49, 3.89) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : 4.10 95% CI: (0.62, 7.58)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Koca, 2009[104] Study design: RCT Trial name: None Study Location: Turkey Health care setting: Physical therapy outpatient clinic Single Site	Total n = 37 Total # of knees = 37 Arm 1, Mean Age: 54.83 (9.27) BMI: 29.64 Arm 2, Mean Age: 55.36 (11.50) BMI: 31.33 Female: 100% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: 2&3, ACR Analgesic Use: Yes, Parecetamol 1500 mg/day	Diagnosis of osteoarthritis of the knee K-L: 2&3 ACR	Concomitant medical problems that prevent participation Prior surgery on one or both knees Injected hyaluronic acid in the past or during the past 6 month(s) Injected corticosteroids in the prior 6 month(s) Prior acute injury to the knee Physical Therapy or Rehab or exercise in the previous 12 month(s) Involvement of the lateral compartment of the knee Meniscopathy Infective or inflammatory pathologies of knee	Arm 1: Control n = 18 Dose: Paracetamol 1500 mg; quadriceps strengthening exercises Frequency: Paracetamol once daily; Duration: 3 months Co-Intervention: Parecetamol and exercise Arm 2: Insole n = 19 Dose: 6 mm wedge Frequency: All day long Duration: 3 months Co-Intervention: Parecetamol and exercise	<u>VAS at rest:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : -1.22 95% CI: (-2.89, 0.45) Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -1.28 95% CI: (-2.84, 0.28) <u>VAS at standing:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : -0.93 95% CI: (-2.25, 0.39) Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -1.16 95% CI: (-2.55, 0.23) <u>VAS at walking:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : -0.62 95% CI: (-2.01, 0.77) Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -1.68 95% CI: (-3.16, -0.20) <u>WOMAC function score:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : -10.06 95% CI: (-19.68, -0.44) Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -11.78 95% CI: (-21.18, -2.38) <u>WOMAC pain score:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : -3.14 95% CI: (-5.96, -0.32) Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -4.02 95% CI: (-6.79, -1.25)
Koca, 2009[104] - Continued					<u>WOMAC total:</u> Follow-Up Time: 1 month : Comparator: Arm 2 vs Arm 1 , MD : -15.16 95% CI: (-28.42, -1.90) Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -17.68 95% CI: (-30.37, -4.99)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Koli, 2015[41] Study design: RCT Trial name: None Study Location: Finland Health care setting: NR Site size: NR	Total n = 80 Age Range: 50-65 Arm 1, Mean Age: 59 (4) BMI: 69.4 (11.7) Arm 2, Mean Age: 58 (4) BMI: 73.4 (9.4) Female: 100% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: Patellofemora 50%, Tibiofemoral 100% Diagnosis: K-L: I-II Analgesic Use: Yes, Table 1: 63% T, 42% C	Diagnosis of osteoarthritis of the knee Duration of Symptoms: Knee pain on most days Minimum Age: >=50 Maximum Age:64 K-L: I-II radiographic tibiofemoral joint OA	Concomitant medical problems that prevent participation Injected corticosteroids in the prior 12 month(s) Intensive exercise more than twice a week Femoral neck bone and lumbar spine bone mineral density (gIcmj2) T-score lower than j2.5 (i.e., indicating osteoporosis), measured with dual-energy x-ray absorptiometry BMI<=35 Knee instability or surgery of the knee caused by trauma Inflammatory joint disease; contraindications to MRI (allergies to contrast agents or renal insufficiency)	Arm 1: Usual care + education / stretching n = 40 Placebo/Usual care Frequency: Every 3 months Duration: 12 months Arm 2: Aerobic exercise n = 38 Dose: 55 min Frequency: 3 times a week Duration: 12 months	<u>KOOS function:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -1.20 95% CI: (-3.53, 1.13) <u>KOOS pain:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -2.60 95% CI: (-6.82, 1.62) <u>KOOS quality of life:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -3.00 95% CI: (-9.40, 3.40)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Kulisch, 2014[73] Study design: RCT Trial name: None Study Location: Hungary Health care setting: Academic rheumatology clinic/department, mineral spa Single Site	Total n = 77 Mean Age: 65.6 Arm 1, Mean Age: 65.5(7.7) BMI: NR Arm 2, Mean Age: 65.6(6.4) BMI: NR Female: 78% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: bilateral 100% Subtype: NR Diagnosis: Mild to moderate Analgesic Use: Yes, Any change in NSAID or chondroprotective therapy during the study was not allowed.	Diagnosis of osteoarthritis of the knee Duration of Symptoms: at least 3 months Minimum Age: 45 Maximum Age:75 ACR: NA Radiographic imaging: NR	Concomitant medical problems that prevent participation Surgery knee limb in prior 6 months month(s) Injected hyaluronic acid in the past or during the past 6 months month(s) Injected corticosteroids in the prior 1 month month(s) Prior acute injury to the knee Physical Therapy or Rehab or exercise in the previous month(s) Severe internal, rheumatic, urogenital, or skin diseases, radiculopathy Conditions for which warm baths were contraindicated Inflammatory rheumatic diseases Effusion Knee fracture or injury in prior 6 months or plate in knee, hip or spine surgery within previous year	Arm 1: Control n = 39 Dose: 30 minutes per session Frequency: 5 days per week Duration: 3 weeks Arm 2: Balneotherapy n = 38 Dose: 30 minutes per session Frequency: 5 days per week Duration: 3 weeks	<u>VAS pain at rest:</u> Follow-Up Time: 15 weeks : Comparator: Arm 2 vs Arm 1 , MD : -16.00 95% CI: (-26.68, -5.32) <u>VAS pain on exertion:</u> Follow-Up Time: 15 weeks : Comparator: Arm 2 vs Arm 1 , MD : -16.60 95% CI: (-25.79, -7.41) <u>WOMAC function:</u> Follow-Up Time: 15 weeks : Comparator: Arm 2 vs Arm 1 , MD : -8.10 95% CI: (-15.82, -0.38) <u>WOMAC pain:</u> Follow-Up Time: 15 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.40 95% CI: (-9.45, 4.65)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Laufer, 2014[82] Study design: RCT Trial name: None Study Location: Israel Health care setting: Physical therapy outpatient clinic Single Site	Total n = 63 Total # of knees = NR Mean Age(SD): 68.9 (SD 7.7) Arm 1, Mean Age: 69.4 (SD 7.7) BMI: 30.5 (SD 5.3) Arm 2, Mean Age: 68.3 (SD 7.7) BMI: 31.4 (SD 6.7) Female: 82.5% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: >=2 Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: knee pain for at least 3 months Minimum Age: 51 Ambulatory K-L: >=2	Concomitant medical problems that prevent participation Prior surgery on one or both knees Injected hyaluronic acid in the past or during the past 6 month(s) Injected corticosteroids in the prior 6 month(s) Physical Therapy or Rehab or exercise in the previous 3 month(s) Pacemaker or medical condition that could affect functional performance Injections to the knee joint during the previous six months Cardiovascular, neurological problems or other orthopedic problems Inability to follow instructions, difficulties with communication and cooperation or schedule inconvenient for them Medical conditions with contraindications for electrical stimulation	Arm 1: Control n = 25 Placebo/Control Dose: NA Frequency: NA Duration: NA Method of Blinding: The person conducting the exercise program was blinded to treatment allocation, blindness of the assessor was not maintained in the posttreatment and follow-up assessments Co-Intervention: Group exercise program delivered biweekly Arm 2: Neuromuscular electrical stimulation n = 25 Dose: Ten contractions were delivered at each session, at maximal tolerated intensity Frequency: Biweekly Duration: 6 weeks Method of Blinding: The person conducting the exercise program was blinded to treatment allocation, blindness of the assessor was not maintained in the posttreatment and follow-up assessments Co-Intervention: Group exercise program delivered biweekly	<u>TUG (s):</u> Follow-Up Time: 18 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.20 95% CI: (-2.32, 1.92) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.20 95% CI: (-1.21, 1.61) <u>VAS pain:</u> Follow-Up Time: 18 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.90 95% CI: (-3.25, -0.55) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.70 95% CI: (-2.70, -0.70) <u>WOMAC total:</u> Follow-Up Time: 18 weeks : Comparator: Arm 2 vs Arm 1 , MD : -14.70 95% CI: (-44.05, 14.65) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -23.20 95% CI: (-43.20, -3.20)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Lim, 2010[63] Study design: RCT Trial name: None Study Location: Korea Health care setting: NR Single Site	Total n = 75 Age Range: >=50 Arm 1, Mean Age: 63.3 (5.3) BMI: 27.7 (2.0) Arm 2, Mean Age: 67.7 (7.7) BMI: 27.6 (1.7) Arm 3, Mean Age: 65.7 (8.9) BMI: 27.9 (1.5) Female: 87% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: II+ Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: >=50 Ambulatory BMI >=25 Abdominal circumferences of more than 90 cm for men and 85 cm for women K-L: II+	Concomitant medical problems that prevent participation Progressive inflammatory or ankylosing states, or had coexisting central nervous system lesions or in adequate cardiac functions Infectious or skin diseases	Arm 1: Control n = 24 Placebo/Education Duration: 8 weeks Method of Blinding: Single-blind Arm 2: Land-based exercise n = 25 Dose: 40 min Frequency: 3 times per week Duration: 8 weeks Method of Blinding: Single-blind Arm 3: Aquatic exercise n = 26 Dose: 40 min Frequency: 3 times per week Duration: 8 weeks Method of Blinding: Single-blind	<u>SF-36 MCS:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -4.50 95% CI: (-11.66, 2.66) Comparator: Arm 3 vs Arm 1 , MD : -6.40 95% CI: (-13.59, 0.79) <u>SF-36 PCS:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -3.50 95% CI: (-8.85, 1.85) Comparator: Arm 3 vs Arm 1 , MD : -1.90 95% CI: (-7.11, 3.31) <u>WOMAC total:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -4.00 95% CI: (-13.64, 5.64) Comparator: Arm 3 vs Arm 1 , MD : -6.70 95% CI: (-15.64, 2.24)
Mahboob, 2009[74] Study design: RCT Trial name: None Study Location: Iran Health care setting: Hospital-outpatient Single Site	Total n = 50 Age Range: 44-79 Arm 1, Mean Age: NR BMI: NR Arm 2, Mean Age: NR BMI: NR Female: 100% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Subtype: NR Diagnosis: ACR, severity not reported Analgesic Use: Yes, During the therapy program, if needed, patients were allowed to take paracetamol in a dose of less than 1500 mg per day(and drug use was assessed at followup).	Diagnosis of osteoarthritis of the knee ACR: not applicable	Prior surgery on one or both knees Injected hyaluronic acid in the past or during the past 6 months month(s) Injected corticosteroids in the prior 6 months month(s) Physical Therapy or Rehab or exercise in the previous 6 months month(s) Effusion Severe CVD and PVD	Arm 1: Placebo n = 25 Placebo/Placebo gel (lacking only mud) Dose: 20 minutes per treatment, each knee Frequency: once per day Duration: 30 days Arm 2: Mudpacks n = 25 Dose: 20 minutes per treatment, each knee Frequency: one treatment per day Duration: 30 days	<u>WOMAC function:</u> Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -13.76 95% CI: (-31.63, 4.11) <u>WOMAC pain:</u> Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -5.44 95% CI: (-11.34, 0.46)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Makovey, 2015[129] Study design: Conference abstract Trial name: Healthy weight for life Study Location: NR Health care setting: Remotely delivered Site size: NR	Total n = 2175 Total # of knees = NR Mean Age(SD): 64 (SD 8.6) Arm 1, Mean Age: 64 (SD 8.6) BMI: 34.4 (SD 5.2) Female: 71% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Analgesic Use: NR	Inclusion : NR	Exclusion : NR	Arm 1: Weight loss n = 2175 Dose: Phase 1 - motivational weight loss utilizing low calorie diet meal replacement, with controlled portions, and free foods for 6 weeks; phase 2 - consolidation weight loss for 6 weeks and phase 3 - short term weight maintenance Frequency: NR Duration: 18 weeks Method of Blinding: NA Co-Intervention: NR	<u>SF-12 Mental Health Composite Score (PCS):</u> Follow-Up Time: 18 weeks : Comparator: <2.5% weight change (post-pre) , MD : 3.58 95% CI: (1.8, 5.4) Comparator: 2.5-5% weight change (post-pre) , MD : 2.38 95% CI: (1.3, 3.5) Comparator: 5.1-7.5% weight change (post-pre) , MD : 5.11 95% CI: (4.2, 6.0) Comparator: 7.6-10% weight change (post-pre) , MD : 5.89 95% CI: (5.0, 6.8) Comparator: >10% weight change (post-pre) , MD : 6.66 95% CI: (5.8, 7.5) <u>SF-12 Physical Health Composite Score (PCS):</u> Follow-Up Time: 18 weeks : Comparator: <2.5% weight change (post-pre) , MD : 3.16 95% CI: (1.7, 4.6) Comparator: 2.5-5% weight change (post-pre) , MD : 4.07 95% CI: (3.2, 5.0) Comparator: 5.1-7.5% weight change (post-pre) , MD : 6.73 95% CI: (6.0, 7.4) Comparator: 7.6-10% weight change (post-pre) , MD : 6.65 95% CI: (5.8, 7.5) Comparator: >10% weight change (post-pre) , MD : 8.60 95% CI: (7.9, 9.3)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Messier, 2013[125] Study design: RCT Trial name: IDEA Study Location: US Health care setting: Single Site	Total n = 454 Mean Age(SD): 66(6) Arm 1, Mean Age: 66(6) BMI: 33.6(3.7) Arm 2, Mean Age: 66(6) BMI: 33.7(3.8) Arm 3, Mean Age: 65(6) BMI: 33.6(3.7) Female: 72% Racial/Ethnic Distribution: Caucasian 81%, Nonwhite 19% Living Situation: Community Dwelling Location of OA: bilateral, unilateral Subtype: Patellofemora, Tibiofemoral Diagnosis: K-L: 2&3, Mild or moderate Analgesic Use: Yes, Patients were allowed to continue using any medications they were taking prior to the study,	Diagnosis of osteoarthritis of the knee: K-L: Minimum Age: 55 Ambulatory Able to sign Consent BMI 27-41 Pain on most days Sedentary lifestyle K-L: 2&3	Concomitant medical problems that prevent participation Prior surgery on one or both knees Knee or hip replacement Heart problems or cancer Injected knee medications Difficulty with ADLs, other knee-related activities >=21 drinks per week	Arm 1: Land-based Exercise n = 150 Placebo/Exercise Dose: 1 hour Frequency: 3 times per week Duration: 18 months Method of Blinding: NR Arm 2: Weight loss n = 152 Dose: 800-1000 calorie deficit per day Frequency: Not applicable Duration: 18 months Method of Blinding: NR Arm 3: Weight loss + land-based exercise n = 152 Dose: 1 hour exercise, 800-1000 calorie deficit Frequency: Exercise 3 times per week Duration: 18 months Method of Blinding: NR	<u>6 min walk (meter):</u> Follow-Up Time: 18 months : Comparator: Arm 2 vs Arm 1 , MD : 23.00 95% CI: (3.15, 42.85) Comparator: Arm 3 vs Arm 1 , MD : -12.00 95% CI: (-33.93, 9.93) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : 28.00 95% CI: (8.90, 47.10) Comparator: Arm 3 vs Arm 1 , MD : -4.00 95% CI: (-24.52, 16.52) <u>SF-36 mental:</u> Follow-Up Time: 18 months : Comparator: Arm 2 vs Arm 1 , MD : 0.50 95% CI: (-1.34, 2.34) Comparator: Arm 3 vs Arm 1 , MD : -0.70 95% CI: (-2.48, 1.08) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : 1.10 95% CI: (-0.88, 3.08) Comparator: Arm 3 vs Arm 1 , MD : -0.80 95% CI: (-2.71, 1.11) <u>SF-36 physical:</u> Follow-Up Time: 18 months : Comparator: Arm 2 vs Arm 1 , MD : 0.00 95% CI: (-2.33, 2.33) Comparator: Arm 3 vs Arm 1 , MD : -2.70 95% CI: (-4.89, -0.51) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -0.30 95% CI: (-2.56, 1.96) Comparator: Arm 3 vs Arm 1 , MD : -2.00 95% CI: (-4.19, 0.19) <u>WOMAC function:</u> Follow-Up Time: 18 months : Comparator: Arm 2 vs Arm 1 , MD : 0.10 95% CI: (-2.67, 2.87) Comparator: Arm 3 vs Arm 1 , MD : -3.40 95% CI: (-6.02, -0.78)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Messier, 2013[125] - Continued					Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : 0.60 95% CI: (-1.88, 3.08) Comparator: Arm 3 vs Arm 1 , MD : -1.20 95% CI: (-3.75, 1.35) <u>WOMAC pain:</u> Follow-Up Time: 18 months : Comparator: Arm 2 vs Arm 1 , MD : 0.40 95% CI: (-0.31, 1.11) Comparator: Arm 3 vs Arm 1 , MD : -0.70 95% CI: (-1.41, 0.01) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : 0.40 95% CI: (-0.32, 1.12) Comparator: Arm 3 vs Arm 1 , MD : 0.10 95% CI: (-0.68, 0.88) <u>Weight (kg):</u> Follow-Up Time: 18 months : Comparator: Arm 2 vs Arm 1 , MD : -6.00 95% CI: (-9.75, -2.25) Comparator: Arm 3 vs Arm 1 , MD : -8.10 95% CI: (-11.92, -4.28) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -6.90 95% CI: (-10.72, -3.08) Comparator: Arm 3 vs Arm 1 , MD : -8.10 95% CI: (-11.85, -4.35)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Miller, 2006[124] Study design: RCT Trial name: None Study Location: US Health care setting: Academic exercise science department Single Site	Total n = 87 Mean Age: 69 Arm 1, Mean Age: 69.3(0.9) BMI: 34.3 (3.9) Arm 2, Mean Age: 69.7 (0.9) BMI: 34.9 (4.9) Female: 62% Racial/Ethnic Distribution: African American 11%, Asian 0%, Caucasian 84%, Hispanic 0%, Native American 2% Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: Symptomatic knee OA Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: 60 BMI>=30 Self-reported difficulty in performing ADLs attributed to knee pain symptomatic knee OA	Unstable medical condition or condition where rapid weight loss or exercise contraindicated Unwillingness to modify diet or physical activity or inability to comply because of food allergy Excessive alcohol consumption	Arm 1: Control n = 43 Placebo/Educational sessions Dose: NA Frequency: two sessions per month Duration: 6 months Method of Blinding: NR Arm 2: Weight loss n = 44 Dose: 60 minutes per session Frequency: 1 session per week Duration: 6 months Method of Blinding: NR Co-Intervention: educational and behavioral sessions	<u>6 min walk (meter):</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -51.00 95% CI: (-96.03, -5.97) <u>BMI:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -2.40 95% CI: (-4.48, -0.32) <u>WOMAC function:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -8.60 95% CI: (-13.50, -3.70) <u>WOMAC pain:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -2.00 95% CI: (-3.25, -0.75) <u>WOMAC total:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -10.70 95% CI: (-17.01, -4.39) <u>Weight (kg):</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -9.10 95% CI: (-16.87, -1.33)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Mizusaki, 2013[83] Study design: RCT Trial name: None Study Location: Brazil Health care setting: Academic rheumatology clinic/department Single Site	Total n = 100 Mean Age: 61 Arm 1, Mean Age: 61.50 ± 6.94 BMI: 29.72 ± 4.11 Arm 2, Mean Age: 60.60 ± 6.72 BMI: 30.08 ± 3.80 Female: 86% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: bilateral 52%, unilateral 48%, NR Subtype: NR Diagnosis: K-L, ACR Analgesic Use: Yes, Patient medication was standardized and not modified during the study period. Paracetamol was prescribed for pain, and diacerein and chloroquine for OA control.	Diagnosis of osteoarthritis of the knee Minimum Age: 50 Maximum Age:74 K-L: >=2 ACR	Physical Therapy or Rehab or exercise in the previous current month(s) Use of a pacemaker, unstable heart conditions Inability to exercise on a stationary bicycle ergometer, inability to walk Diagnosis of fibromyalgia, epilepsy, and skin tumor or lesion at the NMES application site Previous hip or knee arthroplasty	Arm 1: Exercise n = 50 Dose: 40 minutes per session Frequency: two sessions per week Duration: 8 weeks Co-Intervention: a manual including guidelines on how not to overload the knee during daily activities and instructions on the use of ice packs in case of pain and inflammation and warm compresses in case of pain without inflammation Arm 2: NMES n = 50 Dose: 40 minutes per session Frequency: two sessions per week Duration: 8 weeks Co-Intervention: Exercise and a manual including guidelines on how not to overload the knee during daily activities and instructions on the use of ice packs in case of pain and inflammation and warm compresses in case of pain without inflammation	<u>NRS pain score:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.03 95% CI: (-1.12, 1.18) <u>TUG (s):</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.65 95% CI: (-1.25, -0.05) <u>WOMAC function:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.92 95% CI: (-9.14, 3.30) <u>WOMAC pain:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.65 95% CI: (-2.39, 1.09)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Nam, 2014[51] Study design: RCT Trial name: None Study Location: NR Health care setting: Academic orthopedic surgery clinic/department Single Site	Total n = 30 Total # of knees = NR Age Range: NR Arm 1, Mean Age: 63.7 (SD 5.6) BMI: NR Arm 2, Mean Age: 64.9 (SD 6.8) BMI: NR Female: 60% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: > 2 Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: 61 Able to sign Consent Not currently exercising Ability to understand the exercise K-L: >2	Prior surgery on one or both knees	Arm 1: Control n = 15 Placebo/Control Dose: 3 1-min sets, with 1-min breaks between sets for each exercise Frequency: 3 times per week Duration: 6 weeks Method of Blinding: NR Co-Intervention: NR Arm 2: Land-based exercise: Strength/Other n = 15 Dose: 3 times per week Frequency: 3 1-min sets, with 1-min breaks between sets for each exercise Duration: 6 weeks Method of Blinding: NR Co-Intervention: NR	<u>WOMAC total:</u> Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.99 95% CI: (-5.48, -0.50)
Nelson, 2013[90] Study design: RCT Trial name: None Study Location: US Health care setting: NR Single Site	Total n = 34 Mean Age(SD): 55.5 (2.5) Active; 58.4 (2 Arm 1, Mean Age: 58.4 BMI: 34.7 Arm 2, Mean Age: 55.5 BMI: 33.5 Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Analgesic Use: Yes, Unrestricted use of NSAIDs	Diagnosis of osteoarthritis of the knee Duration of Symptoms: 3 months >= 2 h of daily standing activity in a physical occupation Imaging study: Confirmed articular cartilage loss VAS: >=4	Concomitant medical problems that prevent participation Surgery knee limb in prior 6 month(s) Injected hyaluronic acid in the past or during the past 6 month(s) Injected corticosteroids in the prior 6 month(s) Implanted electronic devices On disability or with third party claims	Arm 1: Heat/ultrasound/diathermy n = 19 Placebo/Sham Dose: 15 minutes Frequency: Twice a day Duration: 6 weeks Method of Blinding: Double-blind Arm 2: Heat/ultrasound/diathermy n = 15 Dose: 15 minutes Frequency: Twice a day Duration: 6 weeks Method of Blinding: Double-blind	<u>VAS:</u> Follow-Up Time: 42 days : Comparator: Arm 2 vs Arm 1 , MD : -1.92 95% CI: (-2.35, -1.49)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Oliveira, 2012[47] Study design: RCT Trial name: None Study Location: Brazil Health care setting: Academic rheumatology clinic/department Single Site	Total n = 100 Mean Age: 60 Arm 1, Mean Age: 58.78 (9.60) BMI: 30.00 ± 5.05 Arm 2, Mean Age: 61.50 (6.94) BMI: 29.72 ± 4.11 Female: 92% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: bilateral 25%, unilateral 75% Subtype: NR Diagnosis: K-L: mean: 2 Analgesic Use: Yes, The patients' medication was standardized and not modified during the study.	Diagnosis of osteoarthritis of the knee Minimum Age: 50 Maximum Age:75 K-L: >=2 ACR: NA	Concomitant medical problems that prevent participation Pacemaker use; unstable heart conditions Participation in another exercise program Inability to pedal a stationary bike; inability to walk Previous knee or hip arthroplasty Diagnosis of fibromyalgia; epilepsy; and presence of a tumor or cutaneous lesion that could interfere with the procedure	Arm 1: Control n = 50 Duration: 8 weeks Arm 2: Land-based exercise n = 50 Dose: NR Frequency: two sessions per week Duration: 8 weeks	<u>Lequesne Index:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.98 95% CI: (-3.75, -0.21) <u>TUG:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.80 95% CI: (-2.83, -0.77) <u>WOMAC function:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -5.61 95% CI: (-11.67, 0.45) <u>WOMAC pain:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.77 95% CI: (-2.38, 0.84)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Palmer, 2014[88] Study design: RCT Trial name: None Study Location: UK Health care setting: NR Site size: NR	Total n = 224 Age Range: >=18 Arm 1, Mean Age: 60.9 (10.8) BMI: 29.1 (9.0) Arm 2, Mean Age: 61.2 (11.4) BMI: 29.7 (11.1) Arm 3, Mean Age: 62 (9.4) BMI: 29.8 (7.4) Female: 37% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: ACR Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: >=18 ACR: 3 of 6 signs and symptoms	Concomitant medical problems that prevent participation Prior experience with the intervention of interest Contraindications to TENS	Arm 1: Sham TENS n = 74 Placebo/Sham Dose: As needed; 30 minutes instructional program Frequency: As needed Duration: 6 weeks Method of Blinding: Single-blinded Arm 2: TENS n = 73 Dose: As needed; 30 minutes instructional program Frequency: As needed Duration: 6 weeks Method of Blinding: Single-blinded Co-Intervention: Exercise program Arm 3: Exercise program n = 77 Dose: 1 hour Frequency: Weekly Duration: 6 weeks Method of Blinding: Single-blinded Co-Intervention:	<u>WOMAC function:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 3 , MD : 0.50 95% CI: (-4.16, 5.16) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 3 , MD : 1.30 95% CI: (-3.38, 5.98) <u>WOMAC pain:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 3 , MD : 1.00 95% CI: (-0.92, 2.92) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 3 , MD : -2.00 95% CI: (-3.46, -0.54) <u>WOMAC total:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 3 , MD : 1.00 95% CI: (-5.48, 7.48) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 3 , MD : 1.60 95% CI: (-4.76, 7.96) <u>Clinically significant on WOMAC function:</u> Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 3 , RR : 1.08 95% CI: (0.69, 1.69)
Park, 2013[98] Study design: RCT Trial name: None Study Location: Korea Health care setting: NR Single Site	Total n = 44 Arm 1, Mean Age: 60 (6.22) BMI: 24.8 (1.76) Arm 2, Mean Age: 62.5 (5.66) BMI: 25.3 (2.92) Female: 100 Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Subtype: NR Diagnosis: K-L: 2&3, ACR Analgesic Use: Yes, One control group patient took NSAIDs for a heart condition.	Diagnosis of osteoarthritis of the knee Duration of Symptoms: >= 6 months Minimum Age: >=40 ACR K-L: 2&3	Concomitant medical problems that prevent participation Surgery knee limb in prior 6 month(s) Injected hyaluronic acid in the past or during the past 6 month(s) Injected corticosteroids in the prior 6 month(s) No serious knee trauma in last six months No acute symptomatic OA, comorbidities such as any peripheral or central neuro logic disorders in last 6 months K-L IV	Arm 1: Home-based exercise (HBE) n = 19 Placebo/Control Dose: 10 repetitions of each exercise Frequency: Daily; 3 instructional sessions/week for 8 weeks Duration: 8 weeks Arm 2: Whole body vibration (WBV) n = 17 Dose: 20 minutes Frequency: 3 times a week Duration: 8 weeks	<u>NRS:</u> Follow-Up Time: 2 months : Comparator: Arm 2 vs Arm 1 , MD : -2.00 95% CI: (-3.77, -0.23) <u>WOMAC total:</u> Follow-Up Time: 2 months : Comparator: Arm 2 vs Arm 1 , MD : -3.36 95% CI: (-10.01, 3.29)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Patel, 2013[23] Study design: RCT Trial name: None Study Location: India Health care setting: Academic orthopedic surgery clinic/department Single Site	Total n = 78 Total # of knees = 156 Age Range: 33-80 Arm 1, Mean Age: 53.65 (8.17) BMI: 26.21 (2.93) Arm 2, Mean Age: 53.11 (11.55) BMI: 26.28 (3.23) Arm 3, Mean Age: 51.64 (9.22) BMI: 25.81 (3.31) Female: 70.7% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: bilateral 100% Subtype: NR Diagnosis: Ahlback grade 1-2, ACR Analgesic Use: Yes, Paracetamol 500mg if discomfort	Diagnosis of osteoarthritis of the knee: ACR Ahlback grade: 1-2	Surgery knee limb in prior 12 month(s) Injected hyaluronic acid in the past or during the past 3 month(s) Injected corticosteroids in the prior 3 month(s) Secondary OA due to joint inflammatory diseases, Generalized OA, Advanced stages of OA Metabolic diseases of the bone Coexisting backache Receiving anticoagulant therapy Hemoglobin level less than 10 gm% or associated comorbidities, infection, tumor, crystal arthropathies, or tense joint effusion	Arm 1: Control n = 23 Placebo/Normal saline injection Dose: 8 mL Frequency: Single injection Arm 2: Single PRP Injection n = 27 Dose: 8 mL Frequency: Single injection Co-Intervention: 1 mL of CaCl2 (M/40) was injected in a ratio of 1:4 for every 4 mL of PRP Arm 3: 2 PRP Injections n = 25 Dose: 8 mL Frequency: 2 injections 3 weeks apart Co-Intervention: 1 mL of CaCl2 (M/40) was injected in a ratio of 1:4 for every 4 mL of PRP	<u>VAS:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -2.45 95% CI: (-2.92, -1.98) Comparator: Arm 3 vs Arm 1 , MD : -2.07 95% CI: (-2.59, -1.55) <u>WOMAC function:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -19.38 95% CI: (NC, NC) Comparator: Arm 3 vs Arm 1 , MD : -17.06 95% CI: (NC, NC) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -15.56 95% CI: (NC, NC) Comparator: Arm 3 vs Arm 1 , MD : -16.24 95% CI: (NC, NC) <u>WOMAC pain:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -5.87 95% CI: (NC, NC) Comparator: Arm 3 vs Arm 1 , MD : -4.69 95% CI: (NC, NC) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -5.22 95% CI: (NC, NC) Comparator: Arm 3 vs Arm 1 , MD : -5.10 95% CI: (NC, NC) <u>WOMAC total:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -25.91 95% CI: (NC, NC) Comparator: Arm 3 vs Arm 1 , MD : -22.61 95% CI: (NC, NC) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -21.42 95% CI: (NC, NC) Comparator: Arm 3 vs Arm 1 , MD : -21.82 95% CI: (NC, NC)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Perlman, 2012[121] Study design: RCT Trial name: None Study Location: US Health care setting: Hospital-outpatient Multiple Sites: 2	Total n = 125 Total # of knees = NR Age Range: NR Arm 1, Mean Age: 63.6 (SD 10.2) BMI: 31.7 (SD 6.5) Arm 2, Mean Age: 69.9 (SD 8.6) BMI: 31.0 (SD 7.5) Arm 3, Mean Age: 61.9 (SD 9.5) BMI: 32.1 (SD 6.8) Arm 4, Mean Age: 62.6 (SD 10.6) BMI: 31.8 (SD 6.7) Arm 5, Mean Age: 63.6 (SD 13.0) BMI: 31.3 (SD 7.1) Female: 70.4% Racial/Ethnic Distribution: African American 11.2%, Asian 0.8%, Caucasian 84.8%, Hispanic 0.8%, 0.8% White/Asian, 1.6% Unknown Location of OA: NR Subtype: NR Diagnosis: Met the ACR criteria for knee OA Analgesic Use: Yes, Subjects using NSAIDS or other medications to control pain were included if their doses remained stable 3 months prior to starting the intervention	Minimum Age: 35 Pre-randomization score of 40-90 on the visual analog pain scale Subjects using NSAIDS or other medications to control pain were included if their doses remained stable 3 months prior to starting the intervention	Concomitant medical problems that prevent participation Prior surgery on one or both knees Concomitant or prior use of other meds Injected hyaluronic acid in the past or during the past 1-12 months prior to enrollment month(s) Injected corticosteroids in the prior 1-12 months prior to enrollment month(s) Rheumatoid arthritis, fibromyalgia, recurrent or active pseudogout, cancer, or other serious medical conditions A rash or open wound over the knee and regular use of massage therapy (greater than once a month) Signs or history of kidney or liver failure; unstable asthma; knee replacement of both knees; reported recent use (4 weeks–1 year prior to enrollment) of oral or intra-articular corticosteroids or intra-articular hyaluronate; or knee arthroscopy or significant knee injury one year prior to enrollment	Arm 1: Control (usual care) n = 25, Dose: NR, Frequency: NR, Duration: 8 weeks Method of Blinding: Single-blind, measurements were assessed by separate personnel blinded to treatment assignments Co-Intervention: NR Arm 2: Massage n = 25, Dose: 30 minutes, Frequency: Once per week, Duration: 8 weeks Method of Blinding: Single-blind, measurements were assessed by separate personnel blinded to treatment assignments Co-Intervention: NR Arm 3: Massage n = 25, Dose: 30 minutes, Frequency: 2 times per week for 4 weeks, followed by once per week for 4 weeks, Duration: 8 weeks Method of Blinding: Single-blind, measurements were assessed by separate personnel blinded to treatment assignments Co-Intervention: NR Arm 4: Massage n = 25, Dose: 60 minutes, Frequency: Once per week, Duration: 8 weeks Method of Blinding: Single-blind, measurements were assessed by separate personnel blinded to treatment assignments Co-Intervention: NR Arm 5: Massage n = 25, Dose: 60 minutes, Frequency: 2 times per week for 4 weeks, followed by once per week for 4 weeks	<u>VAS pain:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.90 95% CI: (-17.89, 12.09) Comparator: Arm 3 vs Arm 1 , MD : -2.50 95% CI: (-16.81, 11.81) Comparator: Arm 4 vs Arm 1 , MD : -7.00 95% CI: (-21.09, 7.09) Comparator: Arm 5 vs Arm 1 , MD : -11.30 95% CI: (-27.16, 4.56) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -4.40 95% CI: (-18.27, 9.47) Comparator: Arm 3 vs Arm 1 , MD : -16.30 95% CI: (-30.17, -2.43) Comparator: Arm 4 vs Arm 1 , MD : -30.00 95% CI: (-42.09, -17.91) Comparator: Arm 5 vs Arm 1 , MD : -21.40 95% CI: (-33.42, -9.38) <u>WOMAC function:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -11.10 95% CI: (-22.60, 0.40) Comparator: Arm 3 vs Arm 1 , MD : -3.20 95% CI: (-13.32, 6.92) Comparator: Arm 4 vs Arm 1 , MD : -7.90 95% CI: (-20.05, 4.25) Comparator: Arm 5 vs Arm 1 , MD : -10.20 95% CI: (-21.54, 1.14) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -11.40 95% CI: (-20.90, -1.90) Comparator: Arm 3 vs Arm 1 , MD : -10.60 95% CI: (-21.76, 0.56) Comparator: Arm 4 vs Arm 1 , MD : -14.60 95% CI: (-24.50, -4.70) Comparator: Arm 5 vs Arm 1 , MD : -15.40 95% CI: (-26.48, -4.32)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Perlman, 2012[121] - Continued				Duration: 8 weeks Method of Blinding: Single-blind, measurements were assessed by separate personnel blinded to treatment assignments Co-Intervention: NR	<u>WOMAC global:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -8.30 95% CI: (-19.08, 2.48) Comparator: Arm 3 vs Arm 1 , MD : -1.00 95% CI: (-11.78, 9.78) Comparator: Arm 4 vs Arm 1 , MD : -8.20 95% CI: (-19.46, 3.06) Comparator: Arm 5 vs Arm 1 , MD : -9.10 95% CI: (-21.03, 2.83) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -11.10 95% CI: (-21.34, -0.86) Comparator: Arm 3 vs Arm 1 , MD : -12.10 95% CI: (-23.31, -0.89) Comparator: Arm 4 vs Arm 1 , MD : -17.70 95% CI: (-28.02, -7.38) Comparator: Arm 5 vs Arm 1 , MD : -17.70 95% CI: (-28.50, -6.90) <u>WOMAC pain:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -4.70 95% CI: (-18.04, 8.64) Comparator: Arm 3 vs Arm 1 , MD : 3.60 95% CI: (-8.70, 15.90) Comparator: Arm 4 vs Arm 1 , MD : -6.20 95% CI: (-19.16, 6.76) Comparator: Arm 5 vs Arm 1 , MD : -6.70 95% CI: (-20.19, 6.79) Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -9.50 95% CI: (-20.69, 1.69) Comparator: Arm 3 vs Arm 1 , MD : -8.80 95% CI: (-20.75, 3.15) Comparator: Arm 4 vs Arm 1 , MD : -21.60 95% CI: (-33.47, -9.73) Comparator: Arm 5 vs Arm 1 , MD : -22.10 95% CI: (-33.89, -10.31)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Rabini, 2015[94] Study design: RCT Trial name: None Study Location: Italy Health care setting: Hospital-outpatient Single Site	Total n = 50 Total # of knees = NR Mean Age(SD): 73.72 (SD 5.24) 75.08 (SD Arm 1, Mean Age: 75.08 (SD 5.74) BMI: NR Arm 2, Mean Age: 73.72 (SD 5.24) BMI: NR Female: 78% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: 2&3 Analgesic Use: Yes, Allowed rescue dose the use of 3 g of paracetamol for a maximum of 2 consecutive days.	Diagnosis of osteoarthritis of the knee Duration of Symptoms: chronic knee pain, for at least 3 months Minimum Age: 60 Able to sign Consent K-L: 2&3	Concomitant medical problems that prevent participation Prior surgery on one or both knees Surgery knee limb in prior 24 month(s) BMI > 30 kg/m2 Neurological diseases involving the lower limbs or causing balance problems, systemic inflammatory diseases; severe heart disease; acute infections or bone tuberculosis Arthroprosthesis of lower limbs History of surgery on the affected knee in the last two years Active cancer or anticancer treatment	Arm 1: Sham procedure n = 25 Placebo/Sham procedure Dose: NR Frequency: 10 minutes Duration: NR Method of Blinding: Patients and the researcher responsible of the outcome assessments were unaware of patients' allocation Co-Intervention: Allowed rescue dose of 3g of paracetamol for a maximum of 2 consecutive days and the application of ice package Arm 2: Vibrating platform (whole body vibration) n = 25 Dose: Frequency of 100 Hz and an amplitude of approximately 0.2-0.5 mm for 10 minutes Frequency: 3 doses per day, for 3 consecutive days Duration: NR Method of Blinding: patients and the researcher responsible of the outcome assessments were unaware of patients' allocation Co-Intervention: Allowed rescue dose of 3g of paracetamol for a maximum of 2 consecutive days and the application of ice package	<u>WOMAC total:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -19.04 95% CI: (-27.43, -10.65)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Rayegani, 2014[25] Study design: RCT Trial name: None Study Location: Iran Health care setting: Hospital-outpatient Single Site	Total n = 62 Mean Age(SD): 56.19 (10) Arm 1, Mean Age: 54.68 (10.83) BMI: 27.30 (3.27) Arm 2, Mean Age: 58.07 (8.95) BMI: 28.23 (4.1) Arm 3, Mean Age: BMI: Female: 93.5% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: 1-4, ACR Analgesic Use: Yes, Acetaminophen 500 mg without codeine (up to 2g/day); a single dose of acetaminophen-codeine2 hours before injection	Diagnosis of osteoarthritis of the knee: ACR Duration of Symptoms: 3 months K-L: 1-4	Concomitant or prior use of other meds Analgesics use in the previous3 days month(s) Injected corticosteroids in the prior 3 weeks (systemic in prior 2 weeks) month(s) Prior acute injury to the knee Age > 75 Diabetes mellitus, immunosuppressive and collagen vascular disorders, history of vasovagal shock, history or presence of cancer or malignant disorders, infection or active wound of the knee, Autoimmune and platelet disorders, treatment with anticoagulant and anti-platelet medications 10 days before injection, Hb < 12 g/dL platelet counts < 150,000/mL Pregnancy or breastfeeding Genu valgum/varum greater than 20 degrees	Arm 1: Control n = 31 Method of Blinding: No blinding Co-Intervention: Exercise and acetaminophen 500 mg without codeine Arm 2: Platelet Rich Plasma n = 31 Dose: 4-6 mL Frequency: 2 doses 4 weeks apart Duration: 4 weeks Method of Blinding: No blinding Co-Intervention: Exercise and acetaminophen 500 mg without codeine Arm 3: n = Dose: Frequency: Duration: Method of Blinding: Co-Intervention:	<u>SF-36 mental health:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : 1.00 95% CI: (NC, NC) <u>SF-36 physical health:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : 1.00 95% CI: (NC, NC) <u>WOMAC function:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : 0.17 95% CI: (-5.54, 5.88) <u>WOMAC pain:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -0.96 95% CI: (-2.88, 0.96)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Richette, 2011[131] Study design: Single arm trial Trial name: None Study Location: France Health care setting: Department of Nutrition, Center of Reference for Medical and Surgical Care of Obesity Single Site	Total n = 44 Mean Age(SD): 44 (10.3) Arm 1, Mean Age: 44 (10.3) BMI: 50.7 (7.2) Female: 82% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: 2-4 Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: 1 month K-L: 2-4 VAS: >= 30 mm	Concomitant medical problems that prevent participation Concomitant or prior use of other meds Injected hyaluronic acid in the past or during the past 6 month(s) Injected corticosteroids in the prior 1 month(s) K-L: stage 1 Inflammatory joint disease, chondrocalcinosis of the knee Current use of symptomatic slow-acting drugs, viscosupplementation within the past 6 month	Arm 1: Bariatric surgery n = 44 Duration: 6 months	<u>BMI:</u> Follow-Up Time: 6 months : Comparator: pre-post , MD : 10.30 95% CI: (7.4, 13.2) <u>VAS pain:</u> Follow-Up Time: 6 months : Comparator: pre-post , MD : 25.50 95% CI: (15.5, 35.5) <u>WOMAC function:</u> Follow-Up Time: 6 months : Comparator: pre-post , MD : 371.30 95% CI: (219.6, 523.0) <u>WOMAC pain:</u> Follow-Up Time: 6 months : Comparator: pre-post , MD : 93.20 95% CI: (47.1, 139.3) <u>WOMAC stiffness:</u> Follow-Up Time: 6 months : Comparator: pre-post , MD : 31.80 95% CI: (11.7, 51.9) <u>Weight (kg):</u> Follow-Up Time: 6 months : Comparator: pre-post , MD : 28.60 95% CI: (19.4, 37.8)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Rodrigues, 2008[103] Study design: RCT Trial name: None Study Location: Brazil Health care setting: Academic rheumatology clinic/department Single Site	Total n = 30 Age Range: 45-86 Arm 1, Mean Age: 61.9 (11.3) BMI: 30.6 (3.1) Arm 2, Mean Age: 61.6 (11.4) BMI: 28.9 (3.5) Female: 100% Racial/Ethnic Distribution: Caucasian 50% Living Situation: NR Location of OA: bilateral 100% Subtype: Lateral 100% Diagnosis: K-L: 2-4 Analgesic Use: Yes, If prescribed at least 4 weeks and 8 weeks, respectively, before entry and remained unchanged throughout the study.	Diagnosis of osteoarthritis of the knee K-L: >=2 at lateral compartment K-L: 0&1 at medial compartment VAS on movement: >=2	Prior surgery on one or both knees Injected hyaluronic acid in the past or during the past 6 month(s) Injected corticosteroids in the prior 3 month(s) BMI>=40 Difference in lower limb length > _x0001_1 cm Hallux rigidus History of rheumatologic disease (rheumatoid arthritis, connective tissue disease, microcrystalline arthropathy, and seronegative arthropathy) Soft tissue involvement (anserine, patellar, and calcaneal tendinopathy); foot/lower leg symptoms	Arm 1: Control n = 14 Dose: 3– 6 hours daily Duration: 8 weeks Method of Blinding: Received new shoes with insoles Arm 2: Medial insole n = 16 Dose: 3– 6 hours daily Duration: 8 weeks Method of Blinding: Received new shoes with insoles	<u>Lequesne index:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.40 95% CI: (-5.28, 0.48) <u>VAS movement:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.20 95% CI: (-4.04, -0.36) <u>VAS night:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.50 95% CI: (-3.12, 0.12) <u>VAS rest:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.40 95% CI: (-2.16, 1.36) <u>WOMAC total:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -6.70 95% CI: (-17.09, 3.69) <u>Clinically significant on Lequesne index:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , RR : 0.79 95% CI: (0.59, 1.06)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Rogers, 2012[46] Study design: RCT Trial name: None Study Location: US Health care setting: Home Single Site	Total n = 33 Mean Age: 70 Arm 1, Mean Age: 71.2(10.9) BMI: 30.8 Arm 2, Mean Age: 70.7(10.7) BMI: 28.9 Arm 3, Mean Age: 70.8(6.5) BMI: 28.2 Arm 4, Mean Age: 68.8(10.1) BMI: 29.2 Female: 60% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: bilateral 70%, unilateral 30% Subtype: NR Diagnosis: ACR Analgesic Use: Yes, All participants were advised to continue usual care as prescribed by their physicians, including any use of pain medication, but not to take up any lower extremity exercise program other than the prescribed intervention	Diagnosis of osteoarthritis of the knee Duration of Symptoms: >=1 month Minimum Age: 50 Ambulatory ACR: NA WOMAC function: >=17	Concomitant medical problems that prevent participation Prior surgery on one or both knees Injected hyaluronic acid in the past or during the past prior 4 weeks month(s) Injected corticosteroids in the prior 4 weeks month(s) Physical Therapy or Rehab or exercise in the previous 6 months month(s) Rheumatic disease other than OA Unresolved balance or neurological disorder Major knee trauma, hip or knee arthroplasty, hip or ankly instability or excessive weakness	Arm 1: Control n = 8 Duration: 8 weeks Co-Intervention: Application of intert skin lotion to knees once daily Arm 2: Agility-type exercise n = 8 Dose: 30-40 minutes Frequency: 3 times per week Duration: 8 weeks Co-Intervention: 30-second stic stretches per session Arm 3: Strength/resistance n = 8 Dose: 15 repetitions Frequency: 3 times per week Duration: 8 weeks Co-Intervention: 30-second stic stretches per session Arm 4: Agility- type plus strength/resistance n = 9 Dose: Comparable to individual intervention groups Frequency: 3 times per week Duration: 8 weeks	<u>WOMAC function:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -5.87 95% CI: (-13.22, 1.48) Comparator: Arm 3 vs Arm 1 , MD : -9.62 95% CI: (-19.04, -0.20) Comparator: Arm 4 vs Arm 1 , MD : -11.98 95% CI: (-19.15, -4.81) <u>WOMAC pain:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -3.13 95% CI: (-5.86, -0.40) Comparator: Arm 3 vs Arm 1 , MD : -3.75 95% CI: (-6.39, -1.11) Comparator: Arm 4 vs Arm 1 , MD : -3.00 95% CI: (-5.45, -0.55) <u>WOMAC total:</u> Follow-Up Time: 8 weeks : Comparator: Arm 2 vs Arm 1 , MD : -9.00 95% CI: (-19.79, 1.79) Comparator: Arm 3 vs Arm 1 , MD : -13.62 95% CI: (-26.37, -0.87) Comparator: Arm 4 vs Arm 1 , MD : -15.26 95% CI: (-25.16, -5.36)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Rosedale, 2014[64] Study design: RCT Trial name: None Health care setting: Academic physical therapy clinic/department Single Site	Total n = 158 Mean Age: 65 Arm 1, Mean Age: 64(11) BMI: 30.7(5.3) Arm 2, Mean Age: 64(9) BMI: 32(8.9) Arm 3, Mean Age: 68(10) BMI: 30.6(5.4) Female: 56% Living Situation: Community Dwelling Subtype: NR Diagnosis: Radiological confirmation, not otherwise described Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: > 4 months On knee replacement waiting lists radiologic: NR	Inability to attend exercise-based physiotherapy 2&3 times/week Neurological conditions affecting lower extremities Unable to understand English or provide informed consent	Arm 1: Control n = 59 Duration: NA Arm 2: Land-based exercise, generic n = 59 Dose: 20 minutes Frequency: 4-6 sessions per 2 weeks Duration: 2 weeks Arm 3: Land-based exercise, patient-tailored n = 40 Dose: 20 minutes Frequency: 4-6 sessions per 2 weeks Duration: 2 weeks	<u>KOOS function:</u> Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -9.00 95% CI: (-14.28, -3.72) <u>KOOS pain:</u> Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -10.00 95% CI: (-15.28, -4.72) <u>P4 pain scale:</u> Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -3.00 95% CI: (-5.84, -0.16) <u>Number with improvements in KOOS function score greater than MDC:</u> Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , RR : 0.71 95% CI: (0.39, 1.30) <u>Number with improvements in KOOS pain score greater than MDC:</u> Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , RR : 0.77 95% CI: (0.45, 1.33)
Salacinski, 2012[43] Study design: RCT Trial name: None Study Location: US Health care setting: NR Site size: NR	Total n = 41 Age Range: 37-74 Arm 1, Mean Age: 60.6 (8.4) BMI: 25.7 (6.3) Arm 2, Mean Age: 55.1 (10.5) BMI: 22.4 (3.3) Female: 73% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: K-L: 1-3, Mild to moderate Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: 1 month+ >= 90d degree knee range of motion Stable baseline BP K-L: 1-3 radiographic evidence: of OAK	Concomitant medical problems that prevent participation Personal physician sign off to participate Knee swelling	Arm 1: Usual exercise n = 18 Placebo/Usual care Duration: 12 weeks Arm 2: Cycling n = 19 Dose: 40-60 min Frequency: Twice a week (at least) Duration: 12 weeks	<u>WOMAC function:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : 13.10 95% CI: (3.35, 22.85) <u>WOMAC pain:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : 15.70 95% CI: (6.20, 25.20) <u>WOMAC total:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : 13.20 95% CI: (3.64, 22.76) <u>Knee related qol:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -12.50 95% CI: (-25.60, 0.60)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Samut, 2015[40] Study design: RCT Trial name: None Study Location: Turkey Health care setting: Academic physical medicine/rehab department Single Site	Total n = 42 Age Range: >=50 Arm 1, Mean Age: 60.92 (8.85) BMI: 30.36 (5.67) Arm 2, Mean Age: 62.46 (7.71) BMI: 30.54 (4.45) Arm 3, Mean Age: 57.57 (5.79) BMI: 33.94 (7.33) Female: 100% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: 2&3, ACR Analgesic Use: Yes, All three groups were allowed to take acetaminophen whenever needed.	Diagnosis of osteoarthritis of the knee Sedentary lifestyle (less than 60 min of moderate to high-intensity activity per week) ACR: diagnosis of knee OA K-L: 2&3	Concomitant medical problems that prevent participation Injected hyaluronic acid in the past or during the past 3 month(s) Injected corticosteroids in the prior 3 month(s) Physical Therapy or Rehab or exercise in the previous 3 month(s) Cooperation problems, depression, cognitive impairment, neurologic impairment/disease, orthopedic problems, inflammatory arthritis, cardiovascular problems, end-stage disease, immunosuppressive drug usage, and having an infection or inflammatory condition, pregnancy, and malignant disease. Regular exercise habits	Arm 1: Control n = 13 Placebo/Control Duration: 6 weeks Arm 2: Isokinetic exercise n = 15 Frequency: 3 days week Duration: 6 weeks Arm 3: Aerobic exercise n = 14 Frequency: 3 days a week Duration: 6 weeks	<u>6-min walking test:</u> Follow-Up Time: 6 weeks : Comparator: Arm 3 vs Arm 1 , MD : -45.83 95% CI: (-115.76, 24.10) <u>WOMAC function:</u> Follow-Up Time: 6 weeks : Comparator: Arm 3 vs Arm 1 , MD : -15.35 95% CI: (-24.02, -6.68) <u>WOMAC pain:</u> Follow-Up Time: 6 weeks : Comparator: Arm 3 vs Arm 1 , MD : -4.02 95% CI: (-6.01, -2.03) <u>WOMAC total:</u> Follow-Up Time: 6 weeks : Comparator: Arm 3 vs Arm 1 , MD : -18.58 95% CI: (-29.65, -7.51)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Sattari, 2011[102] Study design: RCT Trial name: None Study Location: Iran Health care setting: Hospital-outpatient Multiple Sites: 3	Total n = 60 Total # of knees = NR Mean Age: 48 years Arm 1, Mean Age: NR BMI: NR Arm 2, Mean Age: NR BMI: NR Arm 3, Mean Age: NR BMI: NR Female: 63% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: Medial 100% Diagnosis: K-L: 3&4 Analgesic Use: Yes, When needed	Diagnosis of osteoarthritis of the knee Minimum Age: 35 Maximum Age:65 Genu varum based on radiographic evidence Complaint of knee pain K-L: 3&4	Prior surgery on one or both knees Surgery knee limb in prior NR month(s) Whole knee degenerative joint disease Symptomatic patellofemoral pain syndrome Rheumatoid arthritis BMI greater than 30 Any superimposed hip or ankle problems	Arm 1: Control group n = 20 Placebo/Control with co-intervention (see below) Dose: NA Frequency: NA Duration: 9 months Method of Blinding: Evaluated by a blind examiner Co-Intervention: Conservative management included activity modification, heating agents at home, straight leg rising and isometric quadriceps home exercises and analgesics when needed Arm 2: Orthotics/orthoses/shoe inserts n = 20 Dose: all the time Frequency: all the time Duration: 9 months Method of Blinding: Evaluated by a blind examiner Co-Intervention: Conservative management included activity modification, heating agents at home, straight leg rising and isometric quadriceps home exercises and analgesics when needed Arm 3: Knee brace n = 20 Dose: Wear it on and off every 2&3 hours for the first week and then put it on as long as possible during the day and take it off at nights Frequency: Daily Duration: 9 months Method of Blinding: Evaluated by a blind examiner Co-Intervention: Conservative management included activity modification, heating agents at home, straight leg rising and isometric quadriceps home exercises and analgesics when needed	<u>VAS pain:</u> Follow-Up Time: 9 months : Comparator: Arm 2 vs Arm 1 , MD : -1.60 95% CI: (-2.31, -0.89) Comparator: Arm 3 vs Arm 1 , MD : -2.80 95% CI: (-3.58, -2.02)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Sawitzke, 2010[28] Study design: RCT Trial name: GAIT Study Location: US Health care setting: NR Multiple Sites: 9	Total n = 662 Age Range: >=40 Arm 1, Mean Age: 56.9 (9.8) BMI: 25.5 Arm 2, Mean Age: 56.7 (10.5) BMI: 27.6 Arm 3, Mean Age: 56.3 (8.8) BMI: 30.2 Arm 4, Mean Age: 56.7 (10.7) BMI: 27.1 Arm 5, Mean Age: 57.6 (10.6) BMI: 25.4 Female: 67.5% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: Tibiofemoral 100% Diagnosis: K-L: 2&3 Analgesic Use: Yes, <= 4000 mg of acetaminophen (Tylenol, McNeil) daily	Diagnosis of osteoarthritis of the knee Duration of Symptoms: 6 months Minimum Age: 40 K-L: 2&3 WOMAC: 125 to 400 mm American Rheumatism Association functional class: 1-3	Concomitant medical problems that prevent participation Prior surgery on one or both knees Prior acute injury to the knee Predominant patellofemoral disease	Arm 1: Placebo n = 131 Placebo/Capsules Frequency: Once daily Duration: 24 months Method of Blinding: Double placebo Arm 2: Glucosamine n = 134 Dose: 500 mg Frequency: 3 times daily Duration: 24 months Method of Blinding: Double dummy Arm 3: Chondroitin n = 126 Dose: 400 mg Frequency: 3 times daily Duration: 24 months Method of Blinding: Double dummy Arm 4: Glucosamine and Chondroitin n = 129 Dose: 500mg and 400 mg Frequency: 3 times daily Duration: 24 months Method of Blinding: Double dummy Arm 5: Celecoxib n = 142 Dose: 200 mg Frequency: Once daily Duration: 24 months Method of Blinding: Double dummy	<u>WOMAC function:</u> Follow-Up Time: 24 months : Comparator: Arm 2 vs Arm 1 , MD : 9.56 95% CI: (-79.79, 98.91) Comparator: Arm 3 vs Arm 1 , MD : 36.64 95% CI: (-64.57, 137.86) Comparator: Arm 4 vs Arm 1 , MD : 54.41 95% CI: (-37.59, 146.41) Comparator: Arm 5 vs Arm 1 , MD : -15.82 95% CI: (-102.31, 70.67) <u>WOMAC pain:</u> Follow-Up Time: 24 months : Comparator: Arm 2 vs Arm 1 , MD : -4.84 95% CI: (-28.29, 18.61) Comparator: Arm 3 vs Arm 1 , MD : 11.50 95% CI: (-15.40, 38.40) Comparator: Arm 4 vs Arm 1 , MD : 1.04 95% CI: (-21.44, 23.51) Comparator: Arm 5 vs Arm 1 , MD : -13.54 95% CI: (-35.92, 8.84)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Schlenk, 2011[42] Study design: RCT Trial name: None Study Location: US Health care setting: Hospital-outpatient Single Site	Total n = 26 Arm 1, Mean Age: 63.2 (9.8) BMI: 33.3(6) Arm 2, Mean Age: 63.2 (9.8) BMI: 33.3(6) Female: 96 Racial/Ethnic Distribution: Caucasian 83%, NR 16% Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: Physician reported Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: 50 Overweight physician confirmation	Concomitant medical problems that prevent participation Pending surgery Prior acute injury to the knee Physical Therapy or Rehab or exercise in the previous currently month(s) Self report of current regular lower extremity exercise program or fitness walking OA of the hip Current participation in a drug trial Contraindications to exercise Inability to use phone, lack of English proficiency, inabiolity to manage own treatment	Arm 1: Control n = 13 Placebo/Usual care Dose: NA Frequency: NA Duration: 6 months Method of Blinding: NR Arm 2: Staying Active with Arthritis (STAR) n = 13 Dose: Initial 1 hour per week sessions of strengthening and flexibility exercise followed by fitness walking Frequency: 150 minutes per week Duration: 6 months Method of Blinding: NR	<u>6-minute walk:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : 22.30 95% CI: (-63.28, 107.88) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : 38.30 95% CI: (-50.86, 127.46) <u>WOMAC function:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -2.70 95% CI: (-12.78, 7.38) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -5.60 95% CI: (-17.65, 6.45)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Segal, 2015[60] Study design: RCT Trial name: None Study Location: US Health care setting: NR Site size: NR	Total n = 58 Age Range: >=60 Arm 1, Mean Age: 69.1 (7.3) Arm 2, Mean Age: 69.6 (6.4) Female: 66% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: I1-4 Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: >=30 days Minimum Age: 60 Ambulatory Mobility disability (LLFDI advanced lower limb function score below 32 points defined using a definite osteophyte or joint space narrowing in either tibiofemoral compartment on posteroanterior knee radiographs16 and an affirmative response to BHave you had pain or stiffness in one or both knees on most of the past 30 days?[on both the telephone screen and screening visit	Concomitant medical problems that prevent participation Injected corticosteroids in the prior 3 month(s) Conditions other than knee OA, which could affect walking, were exclusionary (e.g., amputation, severe back pain, severe peripheral vascular or heart disease and neurological or develop mental disease including multiple sclerosis, Parkinson disease, myositis, rickets, or lower limb musculoskeletal surgery in the past 6 mos). Other prospective exclusion criteria that no volunteers met were as follows: medical conditions that may preclude safe participation in the study protocol, including but not limited to acute or terminal illness or unstable cardiovascular condition (e.g., New York Heart Association class 3&4 congestive heart failure, clinically significant aortic stenosis, history of cardiac arrest, use of a cardiac defibrillator, uncontrolled angina); report of medical conditions that may impair ability to participate including but not limited to pulm Inability or unwillingness to comply with the study protocol or be randomized	Arm 1: Physical therapist directed gait training n = 36 Placebo/Usual care Dose: 45 min Frequency: Twice a week Duration: 3 months Arm 2: Usual care / symptom diary n = 22 Frequency: 1-2 times a week Duration: 3-12 months: To provide a similar frequency of study contact as was provided to the gait-training participants, the control participants were given an Arthritis Foundation symptom diary and instructed to record twice each week for the first 3 mos (Sunday and Wednesday) and once a week Sunday) for the following 9 months: their knee symptoms, healthcare appointments related to their knee OA, or any changes in the way in which they treated their knee OA. The researchers contacted the control participants by telephone at 1, 2, 4, 5, 8, and 10 mos in addition to meeting with them at 3, 6,	<u>KOOS pain:</u> Follow-Up Time: 12 months : Comparator: Arm 2 vs Arm 1 , MD : -7.30 95% CI: (-16.56, 1.96) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -3.70 95% CI: (-12.09, 4.69)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Segal, 2015[60] - Continued			Inability to obtain written clearance for participation in the study by a physician Concurrent participation in another observational or interventional research study; current consumption of more than 14 alcoholic drinks per week; and/or judgment of the principal investigator that participation would endanger the safety of an individual.		
Simao, 2012[97] Study design: RCT Trial name: None Study Location: Brazil Health care setting: Academic exercise physiology lab Single Site	Total n = 31 Mean Age: 72 Arm 1, Mean Age: 71(5.3) BMI: 26.7(2.4) Arm 2, Mean Age: 75(7.4) BMI: 27.4(9.7) Arm 3, Mean Age: 69(3.7) BMI: 29.8(2.53) Female: 86% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: ACR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: most days of previous month Minimum Age: 60 Osteophytes Synovial fluid typical of OA Crepitus Morning stiffness 30 minutes or less ACR: NA K-L: 2	Injected corticosteroids in the prior at least 2 months month(s) Prior acute injury to the knee Physical Therapy or Rehab or exercise in the previous 3 months month(s) Use of any assistive walking device The absence of the minimum clinical and cognitive conditions for performing physical activities Orthopedic disease; neurologic, respiratory, or acute cardiac issues that prevented the performance of the required exercises; vestibular disorders; immunosuppression or immunodeficiency; lack of sphincter control (anal and bladder); or cognitive deficits	Arm 1: Control n = 11 Dose: NA Frequency: NA Duration: NA Arm 2: Vibrating platform n = 10 Dose: NR Frequency: 3 sessions per week Duration: 12 weeks Arm 3: Strength training n = 10 Dose: NR Frequency: 3 sessions per week Duration: 12 weeks	<u>6 min walk:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 3 , MD : -27.40 95% CI: (-84.05, 29.25) <u>WOMAC function:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 3 , MD : -122.50 95% CI: (-551.90, 306.90) <u>WOMAC pain:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 3 , MD : 25.00 95% CI: (-93.83, 143.83)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Simental-Mendia, 2016[27] Study design: RCT Trial name: None Study Location: Mexico Health care setting: Site size: NR	Total n = 75 Age Range: >=18 Arm 1, Mean Age: 55.6 (11.4) BMI: 29.5 (3.8) Arm 2, Mean Age: 57.2 (8.1) BMI: 32.2 (6.2) Female: 65% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: >=3 months Minimum Age: >=18 Multiple: degenerative OA based on a detailed clinical history of knee pain, a complete physical examination and radiologic findings K-L: I-II	Concomitant medical problems that prevent participation Prior surgery on one or both knees Analgesics use in the previouscurrent month(s) Any surgical intervention of the knee, pregnancy, rheumatic disease, hepatological disease, liver disease, severe cardiovascular disease, diabetes, coagulopathy, infection, immunodepression, anticoagulant therapy, and an Hb value \11 g/dL and platelet value \150,000/lL No use of NSAIDs	Arm 1: Acetaminophen n = 32 Placebo/Usual care Dose: 500mg Frequency: Every 8 hrs Duration: 6 weeks Arm 2: Autologous leukocyte-poor platelet-rich plasma n = 33 Frequency: Every 2 weeks Duration: 6 weeks	<u>SF-12 mental component:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.30 95% CI: (-6.10, 1.50) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -7.40 95% CI: (-11.96, -2.84) <u>SF-12 physical component:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -9.90 95% CI: (-14.07, -5.73) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -7.60 95% CI: (-11.72, -3.48) <u>VAS pain:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.20 95% CI: (-3.25, -1.15) <u>WOMAC total:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -12.30 95% CI: (-19.59, -5.01) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -13.40 95% CI: (-20.09, -6.71)
Singh, 2016[50] Study design: RCT Trial name: None Study Location: India Health care setting: NR Site size: NR	Total n = 30 Age Range: >=50 Arm 1, Mean Age: 54.86 (4.35) Arm 2, Mean Age: 55.33 (3.99) Female: 53% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: Medial 100% Diagnosis: K-L: 2&3, ACR, 30mm+ of pain on WOMAC Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: >=6 months Minimum Age: >=50 Ambulatory Medial knee OAK ACR: symptomatic OAK WOMAC: >=30mm of pain while walking K-L: 2&3	Concomitant medical problems that prevent participation Surgery knee limb in prior 6 month(s) Injected corticosteroids in the prior 6 month(s) Lateral tibiofemoral joint space width less than medial Hip OA / hip trauma Systemic arthritic conditions Other lower limb muscular/joint/neurological conditions	Arm 1: Conventional strength training n = 15 Placebo/Usual care Frequency: 5 times a week Duration: 6 weeks Arm 2: Hip adductor exercise n = 15 Frequency: 5 times a week Duration: 6 weeks	<u>6MWT:</u> Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -58.30 95% CI: (-85.68, -30.92) <u>WOMAC function:</u> Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -23.27 95% CI: (-32.73, -13.81)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Somers, 2012[127] Study design: RCT Trial name: OA Life Study Location: US Health care setting: NR Single Site	Total n = 232 Age Range: >=18 Arm 1, Mean Age: 57.94 (10.09) BMI: 34.1 (32.8–35.4) Arm 2, Mean Age: 58.13 (11.25) BMI: 34.4 (33.3–35.5) Arm 3, Mean Age: 58.27 (11.02) BMI: 33.5 (32.4–34.7) Arm 4, Mean Age: 57.47 (9.43) BMI: 34.1 (33.0–35.2) Female: 79 Racial/Ethnic Distribution: 38% Nonwhite, 62% White Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: K-L: 1-4, ACR Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Duration of Symptoms: >=6 months Minimum Age: 18 No other joints affected by OA BMI>=25, =<42 Provider considers OAK a condition that most contributes to limitations Ability to read/speak English ACR K-L: 1-4	Concomitant medical problems that prevent participation Concomitant or prior use of other meds Current use of exercise/weight loss program Other arthritic disorder	Arm 1: Standard care n = 51 Placebo/Standard care Duration: 6 months Method of Blinding: Unblinded Arm 2: Pain coping skills training (PCST) n = 60 Dose: 60 minutes per session Frequency: Weekly / biweekly (first/last 12 weeks) Duration: 6 months Method of Blinding: Unblinded Arm 3: Behavioral weight management (BWM) n = 59 Dose: 60 minutes per session + 3 90 minute exercise sessions per week for first 12 weeks Frequency: Weekly / biweekly (first/last 12 weeks) Duration: 6 months Method of Blinding: Unblinded Arm 4: PCST + BWM n = 62 Dose: 120 minutes per session + 3 90 minutes exercise sessions per week Frequency: Weekly / biweekly (first/last 12 weeks) Duration: 6 months Method of Blinding: Unblinded Co-Intervention: PCST or BWM	<u>BMI:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -0.20 95% CI: (-0.91, 0.51) Comparator: Arm 3 vs Arm 1 , MD : -0.60 95% CI: (-1.24, 0.04) Comparator: Arm 4 vs Arm 1 , MD : -1.80 95% CI: (-2.44, -1.16) <u>WOMAC activity:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -2.30 95% CI: (-7.32, 2.72) Comparator: Arm 3 vs Arm 1 , MD : -1.50 95% CI: (-6.46, 3.46) Comparator: Arm 4 vs Arm 1 , MD : -12.40 95% CI: (-17.29, -7.51) <u>WOMAC pain:</u> Follow-Up Time: 24 months : Comparator: Arm 2 vs Arm 1 , MD : -9.00 95% CI: (-20.25, 2.25) Comparator: Arm 3 vs Arm 1 , MD : -2.00 95% CI: (-13.18, 9.18) Comparator: Arm 4 vs Arm 1 , MD : -14.00 95% CI: (-24.77, -3.23) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -3.50 95% CI: (-8.80, 1.80) Comparator: Arm 3 vs Arm 1 , MD : -2.50 95% CI: (-7.67, 2.67) Comparator: Arm 4 vs Arm 1 , MD : -10.80 95% CI: (-15.77, -5.83) <u>Weight (lbs):</u> Follow-Up Time: 24 months : Comparator: Arm 2 vs Arm 1 , MD : -1.00 95% CI: (NC, NC) Comparator: Arm 3 vs Arm 1 , MD : -5.00 95% CI: (NC, NC) Comparator: Arm 4 vs Arm 1 , MD : -8.00 95% CI: (NC, NC)
Somers, 2012[127] - Continued					Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : 0.30 95% CI: (-3.59, 4.19) Comparator: Arm 3 vs Arm 1 , MD : -4.20 95% CI: (-7.95, -0.45) Comparator: Arm 4 vs Arm 1 , MD : -10.30 95% CI: (-13.92, -6.68)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Stambolova, 2015[34] Study design: RCT Trial name: None Study Location: Bulgaria Health care setting: NR Site size: NR	Total n = 191 Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Analgesic Use: NR	Inclusion : NR	Exclusion : NR	Arm 1: Placebo n = 98 Placebo/Not otherwise described Frequency: Placebo once daily + physiotherapy 30 days a year Duration: 3 years Co-Intervention: Physiotherapy Arm 2: Glucosamine n = 93 Dose: 1500 mg Frequency: GS once daily, 4 months a year; Physiotherapy 30 days a year Duration: 3 years Co-Intervention: Physiotherapy	<u>Change in VAS pain:</u> Follow-Up Time: 3 years : Comparator: Arm 2 vs Arm 1 , MD : -4.60 95% CI: (NC, NC)
Stefanik, 2015[132] Study design: Single arm trial Trial name: None Study Location: US Health care setting: NR Site size: NR	Total n = 23 Age Range: 25-60 Arm 1, Mean Age: 45.7 (8.2) BMI: 41.6 (3.4) Female: 86% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Analgesic Use: NR	Duration of Symptoms: Most days of the month Minimum Age: 25 Maximum Age:59 BMI >=35 Approved for bariatric surgery	Exclusion : NR	Arm 1: Weight loss n = 23	<u>VAS Pain:</u> Follow-Up Time: post surgery : Comparator: pre-post , MD : 5.10 95% CI: (NC, NC) <u>WOMAC Pain:</u> Follow-Up Time: post surgery : Comparator: pre-post , MD : 27.80 95% CI: (NC, NC)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Toda, 2006[108] Study design: RCT Trial name: None Study Location: Japan Health care setting: Orthopedic Rheumatology Clinic Single Site	Total n = 61 Age Range: 63.1-66.4 Arm 1, Mean Age: 66.4 BMI: 25.00 Arm 2, Mean Age: 63.1 BMI: 24.58 Female: 100% Racial/Ethnic Distribution: Asian 100% Living Situation: NR Location of OA: NR Subtype: Medial 100% Diagnosis: ACR Analgesic Use: Yes, Lornoxicam (NSAID) 4mg twice daily	Diagnosis of osteoarthritis of the knee ACR Standing FTA: >176 degrees	Surgery knee limb in prior month(s) Injected corticosteroids in the prior 1 month(s) Prior acute injury to the knee Prior experience with the intervention of interest Steinbrocker 4 Greater or similar reduction in the lateral than the medial femorotibial joint space width Bilateral OA, hip OA, ankle OA Hallux rigidus, valgus deformity of the midfoot, other symptomatic deformities of the foot, advanced arthroplasty of the hindfoot	Arm 1: Traditional shoe insert n = 32 Placebo/Traditional shoe inserts Duration: 6 months Arm 2: Wedge strapped insole n = 29 Duration: 6 months	<u>Lequesne index:</u> Follow-Up Time: 2 years : Comparator: Arm 2 vs Arm 1 , MD : -2.30 95% CI: (-5.45, 0.85) Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -1.50 95% CI: (-4.23, 1.23)
Trombini-Souza, 2013[111] Study design: Conference abstract Trial name: None Study Location: NR Health care setting: NR Site size: NR	Total n = 28 Total # of knees = NR Age Range: NR Arm 1, Mean Age: NR BMI: NR Arm 2, Mean Age: NR BMI: NR Female: 100% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: K-L: 2&3 Analgesic Use: Yes, Paracetamol was permitted, dose unclear	Diagnosis of osteoarthritis of the knee: K-L: 2&3	Physical therapy during the study duration	Arm 1: Control n = 12 Placebo/Control, did not wear similar shoes Dose: NR Frequency: NR Duration: 6 months Method of Blinding: NR Co-Intervention: NR Arm 2: Orthotics/orthoses/shoe inserts n = 16 Dose: NA Frequency: At least 6 hours daily Duration: 6 months Method of Blinding: NR Co-Intervention: NR	<u>WOMAC function:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -37.00 95% CI: (NC, NC) <u>WOMAC pain:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -44.00 95% CI: (NC, NC) <u>WOMAC total:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -37.00 95% CI: (NC, NC)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Trombini-Souza, 2015[112] Study design: RCT Trial name: None Study Location: Brazil Health care setting: Academic rheumatology clinic/department, Physical Therapy Department Single Site	Total n = 56 Age Range: 60-80 Arm 1, Mean Age: 66 (4) Arm 2, Mean Age: 66 (5) Female: 100 Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: Medial 100% Diagnosis: K-L: 2&3, ACR Analgesic Use: Yes	Diagnosis of osteoarthritis of the knee Minimum Age: 60 Maximum Age:79 Ambulatory Able to sign Consent ACR K-L: 2&3 VAS: 3-8	Concomitant medical problems that prevent participation Surgery knee limb in prior 6 month(s) Concomitant or prior use of other meds Injected hyaluronic acid in the past or during the past 6 month(s) Injected corticosteroids in the prior 3 month(s) No leg length discrepancy greater than 1 cm Currently not using the Moleca® or similar shoes for more than 25 hours/week	Arm 1: Waitlist control n = 28 Placebo/Waitlist Duration: 6 months Method of Blinding: Unblinded Arm 2: Orthotic shoe n = 28 Dose: 6 hr/day Frequency: Daily Duration: 6 months Method of Blinding: Unblinded	<u>6 min walk (meter):</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -11.00 95% CI: (-31.81, 9.81) <u>Lequesne index:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -4.20 95% CI: (-6.29, -2.11) <u>WOMAC function:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -43.80 95% CI: (-52.70, -34.90) <u>WOMAC pain:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -38.60 95% CI: (-41.22, -35.98) <u>WOMAC total:</u> Follow-Up Time: 6 months : Comparator: Arm 2 vs Arm 1 , MD : -43.20 95% CI: (-55.77, -30.63)
Tsai, 2013[69] Study design: RCT Trial name: None Study Location: US Health care setting: NR Multiple Sites: 8	Total n = 55 Age Range: >=60 Arm 1, Mean Age: 78.93 (8.30) Arm 2, Mean Age: 78.89 (6.91) Female: 72.7% Racial/Ethnic Distribution: Caucasian 92.7%, 7.3% Other Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: A diagnosis of knee OA based on medical history reviewed with elders or family members/staff and confirmed by a health care provider Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: 60 Ambulatory Able to sign Consent Mild, moderate or subtle cognitive impairment Ability to speak English MD's/NP's permission to participate Verbal Descriptive Scale (VDS): >=2 estern Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Score: 3+	Concomitant medical problems that prevent participation Surgery knee limb in prior 6 month(s) Physical Therapy or Rehab or exercise in the previous 1 month(s) Fractures in last 6 months Falls in last 3 months Vertigo in last month	Arm 1: Attention Control n = 27 Placebo/Attention control Dose: 20-40 minutes (increasing over treatment period) Frequency: 3 sessions/week Duration: 20 weeks Method of Blinding: Unblinded Arm 2: Tai Chi n = 28 Dose: 20-40 minutes (increasing over treatment period) Frequency: 3 sessions/week Duration: 20 weeks Method of Blinding: Unblinded	<u>GUG:</u> Follow-Up Time: 21 weeks : Comparator: Arm 2 vs Arm 1 , MD : 1.15 95% CI: (-0.07, 2.37) Follow-Up Time: 9 weeks : Comparator: Arm 2 vs Arm 1 , MD : 1.54 95% CI: (0.32, 2.76) <u>WOMAC pain:</u> Follow-Up Time: 21 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.58 95% CI: (-2.76, -0.40) Follow-Up Time: 9 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.14 95% CI: (-2.34, 0.06) <u>WOMAC physical:</u> Follow-Up Time: 21 weeks : Comparator: Arm 2 vs Arm 1 , MD : -5.52 95% CI: (-9.70, -1.34) Follow-Up Time: 9 weeks : Comparator: Arm 2 vs Arm 1 , MD : -5.54 95% CI: (-9.72, -1.36)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Wallace, 2006[107] Study design: RCT Trial name: None Study Location: US Health care setting: Academic sport science department Single Site	Total n = 39 Arm 1, Mean Age: 61.0 ± 9.2 BMI: 27.9 ± 4.2 Arm 2, Mean Age: 60.8 ± 9.8 BMI: 28.7 ± 3.7 Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: Medial tibiofemoral 100% Diagnosis: K-L: mean 3.2 Analgesic Use: Yes, Subjects were allowed to continue all medications and other treatments as prescribed by their physicians including over-the-counter or prescription nonsteroidal anti-inflammatory drugs (NSAIDs)	Diagnosis of osteoarthritis of the knee: physician diagnosis of medial tibiofemoral OA Minimum Age: 39 Radiographic medial knee narrowing Mild to moderate pain during walking Pain more than half the days of the month K-L: >=2	Prior experience with the intervention of interest Prior tibial osteotomy or total knee replacement Significant peripheral or central nervous system disease Clinically serious OA of the hip or ankle Requirement for an assistive device to walk	Arm 1: Orthotics n = 18 Dose: NA Frequency: NA Duration: 12 weeks Arm 2: Orthotics n = 18 Dose: NA Frequency: NA Duration: 12 weeks	<u>VAS pain during stair descent:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -19.60 95% CI: (-22.70, -16.50) <u>VAS pain while walking:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -15.10 95% CI: (-25.69, -4.51) <u>WOMAC function:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.39 95% CI: (-7.95, 3.17) <u>WOMAC pain:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -5.00 95% CI: (-10.56, 0.56)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Wang, 2015[95] Study design: RCT Trial name: None Study Location: China Health care setting: Academic rehabilitative medicine clinic/department Single Site	Total n = 99 Arm 1, Mean Age: 61.5±9.1 BMI: 26.7± 1.5 Arm 2, Mean Age: 61.2±9.6 BMI: 26.1 ± 1.2 Female: 72% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling	Diagnosis of osteoarthritis of the knee Duration of Symptoms: at least 3 months Minimum Age: 40 Maximum Age:65 BMI<=30 No previous knee surgeries ACR criteria: NA K-L: 2&3	Surgery knee limb in prior month(s) Any surgery in the preceding year Central nervous system disease, especially epilepsy and serious psychotic disorders History of arthritis (inflammatory or metabolic disease) Deep venous thrombosis in prior 24 weeks Severe heart or lung disease or advanced cancer	Arm 1: Strength/resistance training n = 50 Dose: 3 sets of 10 reps, 40 minutes per day Frequency: 5 days per week Duration: 24 weeks Arm 2: Whole body vibration n = 49 Dose: 30 minutes per day Frequency: 5 days per week Duration: 24 weeks Co-Intervention: quadriceps resistance exercise	<u>6 min walk (meter):</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -77.07 95% CI: (-119.18, -34.96) Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -3.14 95% CI: (-47.01, 40.73) <u>Lequesne index:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.19 95% CI: (-2.30, -0.08) Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.47 95% CI: (-1.59, 0.65) <u>SF-36:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -8.88 95% CI: (-12.03, -5.73) Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.89 95% CI: (-5.03, 1.25) <u>TUG (s):</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -3.01 95% CI: (-3.92, -2.10) Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.26 95% CI: (-1.22, 0.70) <u>VAS pain walking:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.71 95% CI: (-1.21, -0.21) Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.50 95% CI: (-1.10, 0.10) <u>WOMAC function:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.63 95% CI: (-5.63, 0.37)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Wang, 2015[95] - Continued					Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.21 95% CI: (-2.63, 3.05) <u>WOMAC pain:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.49 95% CI: (-3.53, -1.45) Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.45 95% CI: (-1.40, 0.50)
Wang, 2015[96] Study design: RCT Trial name: None Study Location: China Health care setting: Rehab medicine clinic Single Site	Total n = 39 Age Range: NR Arm 1, Mean Age: 61.5 (7.3) BMI: 26.2(2.7) Female: 59% Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: Medial 100% Diagnosis: K-L: NR, ACR Analgesic Use: NR	Diagnosis of osteoarthritis of the knee Minimum Age: 40 Maximum Age:80 Pain predominantly over medial knee Radial evidence of medial compartment KOA Medial joint space narrowing>lateral joint space narrowing Medial compartment osteophyte grade>+lateral osteophyte grade K-L: >=2 ACR	Concomitant medical problems that prevent participation Secondary or inflammatory KOA Ankle, hip, or foot disorders Chronic back pain Alzheimers, Parkinson's, motor neuron disorders, inability to understand procedure Diabetes mellitus, cardiac or respiratory insufficiency	Arm 1: Strength/resistance training n = 20 Dose: NR Frequency: 5 days per week Duration: 12 weeks Arm 2: Vibrating platform	<u>6 min walk (meter):</u> Follow-Up Time: 16 weeks : Comparator: Arm 2 vs Arm 1 , MD : -3.40 95% CI: (-11.12, 4.32) <u>TUG (s):</u> Follow-Up Time: 16 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.30 95% CI: (-3.25, 0.65) <u>VAS pain:</u> Follow-Up Time: 16 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.60 95% CI: (-1.39, 0.19) <u>WOMAC function:</u> Follow-Up Time: 16 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.60 95% CI: (-4.78, 3.58) <u>WOMAC pain:</u> Follow-Up Time: 16 weeks : Comparator: Arm 2 vs Arm 1 , MD : -0.10 95% CI: (-2.17, 1.97)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Wang, 2016[70] Study design: RCT Trial name: None Study Location: US Health care setting: Medical center (inpatient?) Single Site	Total n = 204 Age Range: >=40 Arm 1, Mean Age: 60.1 (10.5) BMI: 32.6 (7.3) Arm 2, Mean Age: 60.3 (10.5) BMI: 33.0 (7.1) Female: 70% (71% T, 69% C) Racial/Ethnic Distribution: African American 39% T, 32% C, Asian 4% T, 2% C, Caucasian 53% (51% T, 55% C), 7% T, 11% C, NR Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: ACR; radiographic evidence of tibiofemoral or patellofemoral osteoarthritis Analgesic Use: Yes, Participants were permitted to continue using routine medications, such as NSAIDs and acetaminophen, and maintain their usual physician visits throughout the study. Participants were not required to discontinue use of their pain medications before formal assessment visits. We kept a written record of changes in use of analgesics and NSAIDs throughout the entire intervention and evaluation period. We did not change or recommend changes in medical therapy.	Diagnosis of osteoarthritis of the knee Minimum Age: >=40 Required to have a score of 40 or greater on at least 1 of the 5 questions in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (range of 0 to 100, with higher scores indicating greater pain) at baseline. ACR: criteria for symptomatic knee osteoarthritis radiographic evidence: d radiographic evidence of tibiofemoral or patellofemoral osteoarthritis (defined as the presence of a definite osteophyte in the tibiofemoral compartment and/or the patellofemoral compartment, as assessed on standing anterior–posterior and lateral or sunrise views)	Concomitant medical problems that prevent participation Prior surgery on one or both knees Injected hyaluronic acid in the past or during the past 6 month(s) Injected corticosteroids in the prior 3 month(s) Prior experience with the intervention of interest Erious medical conditions, such as dementia, symptomatic heart or vascular disease, or recent stroke, that would limit full participation Score less than 24 on the Mini-Mental State Examination	Arm 1: Physical therapy n = 98 Placebo/Usual care Dose: 30 minutes Frequency: Twice a week with physical therapist for 6 weeks; Four times a week with phone followup for last 6 weeks Duration: 12 weeks Method of Blinding: Single-blind Arm 2: Tai chi n = 106 Dose: 60 min Frequency: Twice a week Duration: 12 weeks Method of Blinding: Single-blind	<u>6MWT:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -4.40 95% CI: (-22.30, 13.50) Follow-Up Time: 52 weeks : Comparator: Arm 2 vs Arm 1 , MD : -4.30 95% CI: (-26.02, 17.42) <u>SF-36 mental health:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.10 95% CI: (-3.87, 1.67) Follow-Up Time: 52 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.40 95% CI: (-4.09, 1.29) <u>SF-36 physical health:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -3.70 95% CI: (-6.53, -0.87) Follow-Up Time: 52 weeks : Comparator: Arm 2 vs Arm 1 , MD : -2.00 95% CI: (-4.90, 0.90) <u>WOMAC function:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -131.10 95% CI: (-251.35, -10.85) Follow-Up Time: 52 weeks : Comparator: Arm 2 vs Arm 1 , MD : -88.30 95% CI: (-223.31, 46.71) <u>WOMAC pain:</u> Follow-Up Time: 24 weeks : Comparator: Arm 2 vs Arm 1 , MD : -34.30 95% CI: (-69.74, 1.14) Follow-Up Time: 52 weeks : Comparator: Arm 2 vs Arm 1 , MD : -17.80 95% CI: (-58.18, 22.58)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Wortley, 2013[45] Study design: RCT Trial name: None Study Location: US Health care setting: NR Single Site	Total n = 31 Arm 1, Mean Age: 70.5 (5.0) BMI: 30.0(6.2) Arm 2, Mean Age: 69.5(6.7) BMI: 30.5(6.0) Arm 3, Mean Age: 68.1(5.3) BMI: 35.1(5.9) Female: 22/31 Racial/Ethnic Distribution: NR Living Situation: Community Dwelling Location of OA: NR Subtype: NR Diagnosis: ACR Analgesic Use: Yes, Groups were asked not to alter their regular physical activity or pain medications during the intervention programs	Diagnosis of osteoarthritis of the knee Minimum Age: 60 Maximum Age:85 ACR: NR K-L: 1-4	Injected hyaluronic acid in the past or during the past 3 month(s) Injected corticosteroids in the prior 3 month(s) Arthroscopic surgery within prior 3 months Participated in a resistance training or Tai Ji in the past 6 months Neurological disorders	Arm 1: Control n = 6 Placebo/No activity Dose: NA Frequency: NA Duration: 10 weeks Arm 2: Land-based exercise: strength/resistance n = 13 Dose: 5 or 10 lb. weight, 1 hour per session, two sets of eight repetitions to three sets of 12 repetitions during the first 6 weeks Frequency: 2 sessions per week Duration: 10 weeks Arm 3: Tai Chi n = 12 Dose: 1 hour per session Frequency: 2 sessions per week Duration: 10 weeks	<u>6 min walk:</u> Follow-Up Time: 10 weeks : Comparator: Arm 2 vs Arm 1 , MD : 33.40 95% CI: (-66.24, 133.04) Comparator: Arm 3 vs Arm 1 , MD : 75.60 95% CI: (-26.73, 177.93) <u>TUG (s):</u> Follow-Up Time: 10 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.50 95% CI: (-0.85, 1.85) Comparator: Arm 3 vs Arm 1 , MD : 0.60 95% CI: (-0.91, 2.11) <u>WOMAC function:</u> Follow-Up Time: 10 weeks : Comparator: Arm 2 vs Arm 1 , MD : -235.00 95% CI: (-498.13, 28.13) Comparator: Arm 3 vs Arm 1 , MD : 77.00 95% CI: (-239.40, 393.40) <u>WOMAC pain:</u> Follow-Up Time: 10 weeks : Comparator: Arm 2 vs Arm 1 , MD : -86.00 95% CI: (-180.10, 8.10) Comparator: Arm 3 vs Arm 1 , MD : -16.00 95% CI: (-113.80, 81.80)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Yildirim, 2010[77] Study design: RCT Trial name: None Study Location: Turkey Health care setting: Home, Physical therapy outpatient clinic Site size: NR	Total n = 46 Total # of knees = 80 Age Range: 58.78 Arm 1, Mean Age: 58.78 (SD 9.55) BMI: 29.24 (SD 3.33) Arm 2, Mean Age: 58.78 (SD 10.56) BMI: 30.67 (SD 5.37) Female: 84.8% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: Diagnosed with knee OA according to ACR criteria Analgesic Use: Yes, When recruited, patients underwent an outpatient pharmacological treatment such as NSAID and paracetamol. Patients were allowed to continue routine medication.	Diagnosis of osteoarthritis of the knee Able to sign Consent Literate ACR: Diagnosis of knee OA	Concomitant medical problems that prevent participation Prior acute injury to the knee Acute trauma or inflammation around the leg Cardiac pacemaker Sensitivity or allergy for heat Communication disorder or psychological problems Sensory complications, peripheral vascular diseases, tendency to haemorrhage, oedema on the knee, large scar tissue, malignancy, or deformity to attract the attention during examination or thigh OA	Arm 1: Control n = 23 Placebo/Control, received home visit 2 times Dose: NA Frequency: Visited 2 times Duration: 4 weeks Method of Blinding: NR Co-Intervention: Training guideline with equal information on OA, its effects and treatment based on the available literature Arm 2: Heat n = 23 Dose: 20 minutes Frequency: Visited 15 times Duration: 4 weeks Method of Blinding: NR Co-Intervention: Training guideline with equal information on OA, its effects and treatment based on the available literature	<u>SF-36 pain:</u> Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -10.95 95% CI: (-20.79, -1.11) <u>SF-36 physical function:</u> Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -12.61 95% CI: (-21.49, -3.73) <u>WOMAC function:</u> Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -6.05 95% CI: (-9.65, -2.45) <u>WOMAC pain:</u> Follow-Up Time: 4 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.85 95% CI: (-3.15, -0.55)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Zegels, 2013[37] Study design: RCT Trial name: None Study Location: Belgium, France, Switzerland Health care setting: Hospital-outpatient Multiple Sites: 10	Total n = 352 Age Range: >=45 Arm 1, Mean Age: 64.9 (10.6) BMI: 28.6 (5.3) Arm 2, Mean Age: 65.4 (10.4) BMI: 28.8 (5.2) Arm 3, Mean Age: 65.3 (8.8) BMI: 28.4 (4.4) Female: 64.6% Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Diagnosis: ACR Analgesic Use: Yes, Paracetamol 500 mg up to 4g	Diagnosis of osteoarthritis of the knee: ACR Minimum Age: 45 VAS: >=40mm Lequesne index: >=7	Concomitant medical problems that prevent participation Surgery knee limb in prior 3 month(s) Pending surgery Concomitant or prior use of other meds Injected hyaluronic acid in the past or during the past 6 month(s) Prior experience with the intervention of interest Genu varum or valgum >8 degrees Arthritis and metabolic arthropathies, Paget's illness Pregnancy	Arm 1: Placebo n = 117 Placebo/Matching sachets and capsules Frequency: Sachet once daily, capsule three times daily Duration: 3 months Method of Blinding: Double dummy Arm 2: Chondroitin n = 117 Dose: 1200 mg Frequency: Once daily Duration: 3 months Method of Blinding: Double dummy Arm 3: Chondroitin n = 119 Dose: 400 mg Frequency: 3 times daily Duration: 3 months Method of Blinding: Double dummy	<u>Lequesne function:</u> Follow-Up Time: 2 months : Comparator: Arm 2 vs Arm 1 , MD : -1.50 95% CI: (-2.62, -0.38) Comparator: Arm 3 vs Arm 1 , MD : -1.50 95% CI: (-2.59, -0.41) Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -1.90 95% CI: (-3.11, -0.69) Comparator: Arm 3 vs Arm 1 , MD : -2.20 95% CI: (-3.37, -1.03) <u>VAS pain:</u> Follow-Up Time: 3 months : Comparator: Arm 2 vs Arm 1 , MD : -7.70 95% CI: (-14.43, -0.97) Comparator: Arm 3 vs Arm 1 , MD : -8.30 95% CI: (-15.20, -1.40)

Study	Participants	Inclusion Criteria	Exclusion Criteria	Intervention(s)	Relevant Outcomes Reported
Zhang, 2012[119] Study design: RCT Trial name: None Study Location: US Health care setting: NR Site size: NR	Total n = 36 Age Range: 50-70 Arm 1, Mean Age: 59.86 (4.91) BMI: 28.46 (4.05) Arm 2, Mean Age: 63.47 (2.64) BMI: 28.89 (4.16) Female: 100 Racial/Ethnic Distribution: NR Living Situation: NR Location of OA: NR Subtype: NR Analgesic Use: Yes, Stable use in previous month	Diagnosis of osteoarthritis of the knee Duration of Symptoms: 6 months Minimum Age: 50 Maximum Age:69 Otherwise Healthy Able to sign Consent Female BMI<=35 Health good to satisfactory Pain in the knee in the preceding 2 weeks _3/10 on a Likert pain scale from 1–10, Stable treatment with nonsteroidal anti inflammatory drugs and analgesics in the previous month, (9) if receiving glucosamine, a stable dose for the past 2 months, Unspecified diagnosis of OAK Mild/moderate symptoms of OAK: Most days last month	Concomitant medical problems that prevent participation Injected corticosteroids in the prior 2 month(s) Prior experience with the intervention of interest Knee or hip replacement Current treatment of acupuncture for knee pain Autoimmune dis ease that caused joint pain such as rheumatoid arthritis and lupus Severe unstable chronic illness or terminal dis ease	Arm 1: Usual care n = 21 Placebo/Usual care Duration: 12 weeks Method of Blinding: Unblinded Arm 2: Acupressure n = 15 Dose: 30 minutes Frequency: 5 times a week; 2 training session and 1 conclusion session Duration: 12 weeks Method of Blinding: Unblinded	<u>WOMAC function:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.88 95% CI: (-10.58, 6.82) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -3.40 95% CI: (-12.56, 5.76) <u>WOMAC pain:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : 0.08 95% CI: (-2.36, 2.52) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -1.15 95% CI: (-3.45, 1.15) <u>WOMAC total:</u> Follow-Up Time: 12 weeks : Comparator: Arm 2 vs Arm 1 , MD : -3.74 95% CI: (-15.65, 8.17) Follow-Up Time: 6 weeks : Comparator: Arm 2 vs Arm 1 , MD : -5.51 95% CI: (-16.97, 5.95)

Appendix D. Data Abstraction Tools

1. **Data Abstraction Tool**
2. **Modified Cochrane Risk of Bias Tool**
3. **Modified Newcastle-Ottawa Quality Assessment Scale**
4. **McHarms Tool**

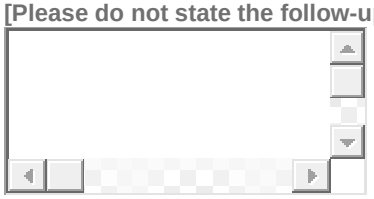
1. Data Abstraction Tool

Does this article report on additional outcomes or followup or post-hoc analysis of a study reported in a separate article?

- ● Yes (specify ID or reference) [ ]
- ● No

Clear Response

If this is a follow-up to a study reported in another article, then what is the follow-up time for this article? [Please do not state the follow-up time for the original article]



If this is part of a named trial or study, please specify the name?

- ☐ CAROT
- ☐ GAIT
- ☐ IDEA
- ☐ OAI
- ☐ LEGS
- ☐ OA Life
- ☐ impact-p
- ☐ Healthy weight for life
- ☐ LIGHT

- [ ] Osteoarthritis Chronic CAre Program (OACCP)
- [ ] MOVES
- [ ] Osteoarthritis of the Knee Self- Management Program
- [ ] Osteoarthritis Before and After Bariatric Surgery (OABS) Study
- [ ] Physical Activity, Inflammation, and Body Composition Trial

Permanently add an answer to this question

Do you need another article to complete this form?

- ● Yes (stop until Aneesa links the article; specify reference number) [ ]
- ● No

Clear Response

Study Design

- ● Systematic review or meta-analysis (skip to intervention) **(STOP)**
- ● Randomized controlled
- ● Weight loss single arm trial
- ● Observational cohort or case series for weight loss, self-managed care, or adverse events
- ● Single arm trial NOT for weight loss **(STOP)**

- Conference abstract
- Controlled Clinical Trial **(STOP)**

Clear Response

Location(s):

- Canada
- China
- Germany
- Iran
- Korea
- Russia
- Turkey
- USA
- Not Reported
- Other (specify)

Health care Setting:

- Academic orthopedic surgery clinic/department

- [ ] Academic rheumatology clinic/department
- [ ] Aquatic center
- [ ] Gym-self managed
- [ ] Home
- [ ] Home-pool
- [ ] Hospital-inpatient
- [ ] Hospital-outpatient
- [ ] Physical therapy outpatient clinic
- [ ] Primary care practice
- [ ] Rehab/skilled nursing facility
- [ ] Other
- [ ] Not Reported

Is this a single center or multicenter study?

- ● Single center
- ● Multicenter study [speciy how many sites]
- ● NR

Clear Response

Participants (living situation):

- ☐ Community dwelling
- ☐ Institutionalized
- ☐ Hospitalized
- ☐ Rehab-inpatient
- ☐ Not Reported

Participants (race/ethnicity):
Average the number and put % after
For other, please indicate as "20% Korean"

- ☐ % African American
- ☐ % Asian
- ☐ % Caucasian
- ☐ % Hispanic
- ☐ % Latino
- ☐ Other 1 (specify race and %)
- ☐ Other 2 (specify race and %)

☐ Other 3 (specify race and %) ____

☐ Other 4 (specify race and %) ____

☐ Other 5 (specify race and %) ____

☐ NR

Participants:
Average the number and put % after

☐ Age range: ___ to ___ (specify range) ____

☐ Number of participants enrolled (specify number) ____

☐ Number of knees if analyzed that way (specify) ____

☐ % female (specify %) ____

Location of OA [if % specified, record]:

☐ Bilateral knee OA [specify %, if given] ____

☐ Unilateral knee OA [specify %, if given] ____

☐ Not reported

Subtype location [if % specified, record]

☐ Medial [specify %, if given] ____

☐ Lateral [specify %, if given]

☐ Patellofemoral [specify %, if given]

☐ Tibiofemoral [specify %, if given]

☐ Other (specify type and %)

☐ Not Reported

Diagnosis

☐ Kellgren-Lawrence stages, (specify number: e.g., III-IV)

☐ Other severity measure (e.g., mild-to-moderate)

☐ Other criteria (e.g., ACR)

Were participants allowed to continue use of analgesics?

● Yes

● No

● NR

Clear Response

Inclusion criteria for participation in the study:

☐ Diagnosis of osteoarthritis of the knee (specify diagnostic modality and cutoff scores, if relevant)

- [ ] Duration of symptoms
- [ ] Age >= ___ (specify inclusion of age)
- [ ] Age < ___ (specify inclusion of age)
- [ ] Ambulatory
- [ ] Otherwise healthy
- [ ] Able to sign consent/no mental or cognitive problems
- [ ] Other 1 (specify)
- [ ] Other 2 (specify)
- [ ] Other 3 (specify)
- [ ] Other 4 (specify)
- [ ] Other 5 (specify)
- [ ] Not Reported

Exclusion criteria for the study:

- [ ] Concomitant medical problems that prevent participation
- [ ] Prior surgery on one or both knees
- [ ] Surgery on the knee/limb in the prior __ months (specify how many months)

- ☐ Pending surgery on the knee
- ☐ Concomitant or prior use of other medication
- ☐ Injected hyaluronic acid in the past or during the past ___ months (specify how many months) ☐
- ☐ Analgesic use in the previous ___ months (specify how many months) ☐
- ☐ Injected corticosteroids in the prior ___ months (specify how many months) ☐
- ☐ Prior acute injury to knee
- ☐ Continued use of analgesics
- ☐ Physical therapy or rehab or exercise in the previous ___ months (specify how many months) ☐
- ☐ Prior experience with the intervention of interest
- ☐ Other 1 (specify) ☐
- ☐ Other 2 (specify) ☐
- ☐ Other 3 (specify) ☐
- ☐ Other 4 (specify) ☐
- ☐ Other 5 (specify) ☐
- ☐ Not Reported

Arms

How many arms are there?

- ● 1
- ● 2
- ● 3
- ● 4
- ● 5
- ● 6

Funding:

- ☐ Government
- ☐ Private foundation
- ☐ Manufacturer
- ☐ Other funding (specify) ☐
- ☐ NR

Did the authors have any conflict of interest?

- ● The article reported that some or all of the authors had conflict of interest (such as employment by, or consultation for, the manufacturer of the intervention)

- The article stated that authors had no conflict of interest
- The article did not mention author conflict of interest

Clear Response

2. Modified Cochrane Risk of Bias Tool

Cochrane Risk of Bias Tool

Selection Bias

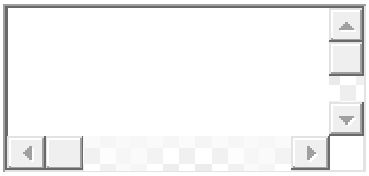
1. Was the allocation sequence adequately generated (e.g., rand number table, computer-generated randomization)

There is a LOW RISK OF BIAS if the investigators describe a random component in the sequence generation process such as: referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots. There is a HIGH RISK OF BIAS if the investigators describe a non-random component in the sequence generation process, such as: sequence generated by odd or even date of birth, date (or day) of admission, hospital or clinic record number; or allocation by judgement of the clinician, preference of the participant, results of a laboratory test or a series of tests, or availability of the intervention. IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.

- ● Low risk (yes)
- ● High risk (no)
- ● Unclear

Clear Response

High risk notes



2. Was ALLOCATION adequately concealed (prior to assignment)?

There is a LOW RISK OF BIAS if the participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomization); sequentially numbered drug containers of identical appearance; or sequentially numbered, opaque, sealed envelopes. There is a HIGH RISK OF BIAS if participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; or other explicitly unconcealed procedures. IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.

- ● Low risk

- High risk
- Unclear

Clear Response

High risk notes

Performance bias

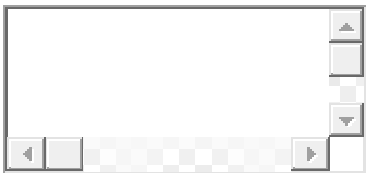
3. Were PARTICIPANTS or THE HEALTH CARE PROVIDER who administered the intervention adequately BLINDED?

There is a LOW RISK OF BIAS if blinding of participants was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.

- Low risk
- High risk
- Unclear

Clear Response

High risk notes



Detection Bias

4. Were OUTCOME ASSESSORS adequately BLINDED?

There is LOW RISK OF BIAS if the blinding of the outcome assessment was ensured and it was unlikely that the blinding could have been broken; or if there was no or incomplete blinding, but the outcome is unlikely to be influenced by lack of blinding (ie, lab tests--lipids--inherently low risk of bias, but not blood pressure).

- Low risk
- High risk
- Unclear

Clear Response

High risk notes

Attrition bias

5. Incomplete outcome data (ATTRITION BIAS) due to amount, nature or handling of incomplete outcome data

There is a LOW RISK OF BIAS if there were no missing outcome data; reasons for missing outcome data were unlikely to be related to the true outcome; missing outcome data were balanced in numbers, with similar reasons for missing data across groups (****The percentage of withdrawals and drop-outs should not exceed 20% for short-term follow-up [<=1 year] and 30% for long-term follow-up [>1 year]****). IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.

- Low risk
- High risk
- Unclear

Clear Response

High risk notes

Reporting bias

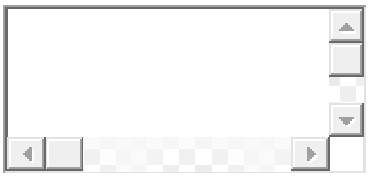
6. Is there evidence of SELECTIVE OUTCOME REPORTING bias?

Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? The authors can refer to a published protocol or to another study. Select high risk if they list outcomes for which they report no data, do not refer to another article for that outcome, or don't mention a published (posted) protocol, OR if they say they used something like the WOMAC but report only the outcome for, say, pain or function.

- ● Low risk
- ● High risk
- ● Unclear

Clear Response

Notes



Other bias

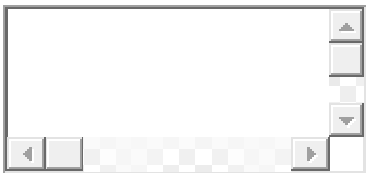
7. INTENTION-TO-TREAT analysis? (Yes/No)

YES if they state ITT and methods used were actually ITT, or **all** participants were analyzed in the group to which they were allocated by randomization (no cross-over). IF NO ITT, EXPLAIN IN NOTES.

- ● Yes
- ● No
- ● Unclear

Clear Response

Notes



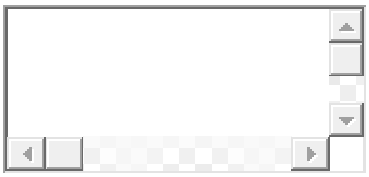
8. Group SIMILARITY AT BASELINE (GENERAL**)**

There is LOW RISK OF BIAS if groups are similar at baseline for demographic and other factors (e,g, BMI, baseline pain). Also LOW risk of bias if any baseline differences were adjusted for in all relevant analyses. IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.

- ● Low risk
- ● High risk
- ● Unclear

Clear Response

Notes



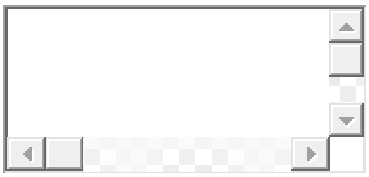
9. Was there incomplete adherence/COMPLIANCE with interventions across groups?

There is LOW RISK OF BIAS if compliance with the interventions was acceptable (>=80% across intervention duration), based on the reported actual compliance compared to protocol or increased biomarker levels were reported during or at the end of the intervention. There is HIGH RISK OF BIAS if compliance was low (<80%). There is UNCLEAR RISK OF BIAS if these data were not reported.

- ● Low risk
- ● High risk
- ● Unclear

Clear Response

Notes



10. Additional Bias: Did authors report a power calculation and did they achieve adequate n?

- Yes
- No

3. Modified Newcastle-Ottawa Quality Assessment Scale

Selection

1) Representativeness of the exposed cohort

- [ ] a) truly representative of the average pregnant women and children in the community
- [ ] b) somewhat representative of the average pregnant women and children in the community
- [ ] c) selected group of users eg nurses, volunteers
- [ ] d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

- [ ] a) drawn from the same community as the exposed cohort
- [ ] b) drawn from a different source
- [ ] c) no description of the derivation of the non exposed cohort
- [ ] d) N/A

3) Ascertainment of exposure

- [ ] a) secure record (eg surgical records)
- [ ] b) structured interview
- [ ] c) written self report
- [ ] d) no description

4) Demonstration that outcome of interest was not present at start of study (if relevant, which will almost never be the case) or author's statement that a valid outcome measure was chosen.

● a) yes

● b) no

Clear Response

Comparability
1) Comparability of cohorts on the basis of the design or analysis

If the authors describe factors for which they adjusted or noted that cohorts were matched on important factors and listed the factors, count that as a “yes.”

☐ a) study controls for _____ (select the most important factor)

☐ b) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.)

Outcome
1) Assessment of outcome

☐ a) independent blind assessment

☐ b) record linkage

☐ c) self report

☐ d) no description

2) Was follow-up long enough for outcomes to occur (e.g., 5 years or older for asthma; for other outcomes, if the authors say why they chose a particular followup time, definitely select "yes"; otherwise use your own judgment.

● a) yes (select an adequate follow up period for outcome of interest)

● b) no

Clear Response

3) Adequacy of follow up of cohorts

☐ a) complete follow up - all subjects accounted for

☐ b) subjects lost to follow up unlikely to introduce bias - small number lost - >80% retention for ≤ 1 year followup; >30% retention for 1-5 years followup; >40% retention for 6-10 years followup; >50% retention for 11-18 years followup; or description provided of those lost)

☐ c) follow up rate < 80% (select an adequate %) and no description of those lost

☐ d) no statement

4. McHarms Tool

1. Were the harms PRE-DEFINED using standardized or precise definitions?

Harms can be defined as the totality of adverse consequences of an intervention or therapy. Harms are the opposite of benefits, against which they are directly compared. The balance between the benefit(s) and harm(s) of an intervention (i.e. drug or surgery) is ideally used to determine its efficacy or effectiveness.

Pre-defined indicates that the harms that were expected are explicitly defined prior to the collection of these expected events. For example, if bleeding is listed as a harmful event, the criteria by which they determine the bleeding (i.e. body location, type, or amount of blood loss that counts as an event, etc) should be specified.

Standardized classification of harms can be derived from any of the following:

1) reference to standard terminology or classifications of harms from a recognized external organization(s)(such as government regulatory or health agencies. Examples of standardized terminology for harms includes, WHO-ART, MEDra, HTA report on the Measurement and Monitoring of Surgical Adverse Events)

2) previously explicitly defined classifications of harms in the literature, or

3) based on pre-specified clinical criteria, or

4) pre-specified laboratory test (may not need to have a specific cut-off level specified in all cases)

In some instances only some of the harms identified in a study will be precisely defined. In this case, there must be some judgement.

- ● Yes
- ● No
- ● Unclear

Clear Response

2. Was the mode of harms collection specified as ACTIVE?

Active ascertainment of harms indicates that participants are asked about the occurrence of specific harms in

structured questionnaires or interviews or pre-defined laboratory or diagnostic tests and usually performed at pre-specified time intervals.

Passive ascertainment of harms indicates that study participants spontaneously report (on their own initiatives) or are allowed to report harmful events not probed with active ascertainment.

- Yes
- No
- Unclear

Clear Response

3. Was the potential occurrence of harmful events collected at pre-specified intervals; for example, the occurrence of post-operative complications were evaluated on a daily basis within 30 days of the surgery?

- Yes
- No
- Unclear

Clear Response

4. Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?

For example, the study reported 3 types of harmful events (nausea, vomiting, and bleeding); for each of these events the frequency was reported for each study group.

- Yes
- No
- Unclear

Clear Response

5. Was the TOTAL NUMBER of participants affected by harms specified for each study arm?

- Yes
- No
- Unclear

Clear Response

6. If the study reported that there were no serious AE's reported did they define serious AEs?

- Yes
- No
- Unclear
- N/A

Clear Response

Appendix E. Strength of Evidence

Table E1. Strength of evidence

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
KQ 1 Platelet-rich plasma							
Short-term pain (KOOS, WOMAC)	2 RCTs	Single or dual injections vs. saline: MD -5.22 Single injection PRP vs. paracetamol: no difference	Moderate, unclear	Inconsistent	Direct	imprecise	Insufficient evidence
Short-term function	1 RCT	Single or dual injections vs. saline: MD –15.56	Moderate	NA	Direct	Not reported	Insufficient evidence
Short-term WOMAC total	2 RCTs	Single or dual injections vs. saline: (MD –21.42) (MD –13.4, 95% CI –20.00, –6.71)	Moderate	NA	Direct	Not reported	Insufficient evidence
Short-term QoL (SF-12 physical)	1 RCT	SF-12 (MD –7.60, 95% CI –11.76, –3.48)	Low				
Medium-term pain	5 RCTs	Single injection vs. saline: Significant benefit Dual injections vs. saline: significant benefit Dual injections vs. TAU: no effect Single injection vs. analgesic: significant benefit	2 High, Moderate, 2 low	Consistent	Direct	Precise	Low for a positive effect of PRP on medium term pain
Medium-term function	2 RCT	Injection vs. saline: benefit Injection vs. TAU: no benefit	Moderate	NA	Direct	Not reported	Insufficient evidence
Medium term WOMAC total	2 RCT	Single or dual injections vs. saline: significant benefit in 1 RCT	Moderate, low	Unclear	Direct	Not reported	Insufficient

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		–					
Medium term SF-36 physical domain	1 RCT	Injection vs. TAU Unclear	High	NA	Direct	Not reported	
Medium term EQ-5d	1 RCT	Significant improvement with 1 or 2 injections	Low	NA	Direct	Precise	
Long-term pain	0						Insufficient evidence
Long-term function	0						Insufficient evidence
Long-term other	0						Insufficient evidence
Glucosamine plus chondroitin							
Medium term pain	2 RCTs		High, low, low	Inconsistent	Direct	Precise	Low for an effect of glucosamine-chondroitin on medium-term pain(3 studies: one head to head, one placebo-controlled, one open)
	1 RCT (n=603)	WOMAC, VAS: no difference glucosamine sulfate-chondroitin celecoxib in non-inferiority trial and response met MCID	Low	N/A	Direct	Precise	
		WOMAC MD –1.59(–2.31, –0.87); VAS MD–2.08 (–2.40, –1.76)	High	N/A	Direct	Precise	
	1 RCT (n=164)	Placebo-controlled	Low	N/A	Direct	Precise	
Medium term function	3 RCTs	Significant benefit in 2/3 RCTs	2 low, 1 moderate	Inconsistent	Direct	Precise	Low for an effect of glucosamine-chondroitin on medium term function
Medium-term other	2 RCTs	No impact on	High, low	Inconsistent	Direct	N/R	Insufficient

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
outcomes		WOMAC stiffness in 1 RCT, but improvement in 2nd RCT, No impact on Eq-5D					
Long-term pain	3 RCTs (n=466 in pooled analysis)	WOMAC (SMD -0.73, 95% CI −4.03; 2.57; I^2 97%)	High, 2 low	Inconsistent	Direct	Precise	Moderate for no effect of glucosamine-sulfate on long-term pain
Long-term function	3 RCTs (n=466 in pooled analysis)	WOMAC function – (SMD 0.45, 95% CI −2.75; 1.84; I^2 95%)	High, 2 Low	Inconsistent	Direct	Precise	Low for no effect of glucosamine on long-term function
Long-term other outcomes	2 RCTs	Significant effect on long-term WOMAC stiffness; LEGS trial showed no effect compared with placebo on long-term SF-12 physical domain					Insufficient evidence
Glucosamine							
Short-term pain	0 RCTs						Insufficient evidence
Short-term function	0 RCTs						Insufficient evidence
Short-term other	0 RCTs						Insufficient evidence
Medium-term pain	0 RCTs						Insufficient evidence
Medium-term function	0 RCTs						Insufficient evidence
Medium-term other	0 RCTs						Insufficient evidence
Long-term pain	3 RCTs (n=1007 in pooled analysis)	WOMAC (SMD -0.05, 95% CI −0.22; 0.12; I^2 0%)	High, 2 low	Inconsistent	Direct	Precise	Low for beneficial effect on pain vs. analgesic or placebo at 102 years
Long-term function	3 RCTs	GAIT Trial: comparable to analgesic LEGS Trial: no effect cf. placebo Bulgarian study:	High, 2 low	Inconsistent	Direct	Precise	Low for no consistent benefit

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		significant benefit cf. placebo					
Long-term other outcomes	2 RCTs	GAIT trial: positive impact on OMERACT-OARSI scores LEGS Trial SF-12 physical domain scores not improved	2 Low				Insufficient evidence
	2 pooled RCTs	Risk for undergoing TKR decreased by more than 50% with glucosamine supplementation vs. placebo	Low				Insufficient evidence
Chondroitin-sulfate							
Short-term pain	1 RCT (n=353)	Zegels trial: 2 dosing strategies vs. placebo VAS pain: no differences between doses or vs. placebo	Low	Consistent	Direct	Precise	Low for no effect of chondroitin on short-term pain
Short-term function	1 RCT (n=353)	Zegels trial: significant improvement in Lequesne scores vs. placebo (p=0.003)	Low	Consistent	Direct	Precise	Low for significant effect of chondroitin on short-term function
Medium-term pain	2 RCTs (n=975)	Zegels trial: VAS pain significantly improved by both dosing strategies STOPP Trial: benefit on WOMAC and VAS	2 Low	Consistent	Direct	Precise	Low for an effect of chondroitin on medium-term pain
Medium-term function	2 RCTs		9, 10/10	Inconsistent	Direct	Precise	Insufficient evidence
		Zegels trial: significant improvement in Lequesne scores vs. placebo for both dosing strategies:	10/10	N/A	Direct	Precise	

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		STOPP Trial found no difference in WOMAC function vs. placebo	9/10	N/A	Direct	Precise	
Long-term pain	3 RCTs	STOPP Trial, GAIT Trial, and LEGS Trial showed no effect vs. placebo	3 Low	Consistent	Direct	Precise	Moderate for no long-term effect of chondroitin sulfate on pain
Long-term function	2 RCTs	GAIT Trial, and LEGS Trial showed no effect vs. placebo	2 Low	Consistent	Direct	Precise	Low for no significant effect of chondroitin on long-term function
Long-term other	1 RCT	STOPP Trial showed no significant between-group difference in analgesic use	9/10	N/A	Direct	Precise	Insufficient evidence
Strength/resistance Training							
Short-term pain	5 RCTs (n=215 in pooled analysis)	5 pooled RCTs (n=160) **SMD -0.55 (95% CI −1.46, 0.37)**	Unclear-low	Inconsistent	Direct	Imprecise	Low for no significant effect of strength training on short-term pain
Short-term function	5 RCTs (n=245 in pooled analysis)	5 pooled RCTs **SMD -0.60 (95% CI −1.38, 0.17)**	Unclear-low	Inconsistent	Direct	Imprecise	Low for no significant effect of strength training on short-term function
Short-term WOMAC total	3 RCTs	Significant between-group differences		Consistent	Direct	Precise	Moderate for short-term effect of strength training on WOMAC total
	2 RCTs	TUG	High, low	Inconsistent	Direct	Precise	Insufficient evidence
	2 RCTs	SF-36	Moderate, low	Consistent	Direct	Precise	Insufficient evidence
	1 RCT	6-minute walk	High	N/A	Direct	Precise	Insufficient evidence
Medium-term pain	2 RCTs	No improvements in pain when combined with PCST vs. PCST alone or when compared with other	Moderate, low	Consistent	Direct	Precise	Insufficient evidence

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		active controls					
Medium-term function	3 RCTs (n=187 in pooled analysis)	SMD −0.43, 95% CI −2.16, 1.30	Moderate, low	Inconsistent	Direct	Precise	Low SoE for a non-significant beneficial effect
Medium-term other	1 RCT	No effect on SF-36 physical domain	Moderate	N/A	Direct	Precise	Insufficient evidence
Long-term pain	1 RCT	Significant improvements in VAS and WOMAC pain	Low	N/A	Direct	Precise	Insufficient evidence
Long-term function	1 RCT	Significant improvement in WOMAC function with strength+ PCST vs. PCST alone	Low	N/A	Direct	Precise	Insufficient evidence
Agility Training							
Short-term pain	3 RCTs	3 different pain measures: 2/3 showed significant improvement cf. TAU and third showed no difference from strength training	Low-high	Inconsistent but consistent vs. passive controls	Direct	Precise	Low for an effect on short-term pain
Short-term function	3 RCTs	2 different function measures	2 moderate, 1 low	Inconsistent	Direct	Precise	Low for no effect on short-term function
Short-term other	3 RCTs	3 different outcome measures: each showed significant improvement	5/10	N/A	Direct	Precise	Insufficient evidence
Medium-term pain	3 RCTs	NRS: no significant difference in pain KOOS pain: significant improvement vs. no-attention control	Low-high	Inconsistent	Direct	Precise	Low for no effect on medium-term pain
Medium term function	2 RCTs	WOMAC function: no difference vs. strength training		N/A	Direct	Precise	Low for no effect on medium-term function

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
Medium-term other	2 RCTs	TUG improvement comparable to strength training; walking speed improved for water-based agility training but not land-based agility training vs. control	Low, high	N/A	Direct	Precise	Insufficient evidence
Long-term pain	3 RCTs	2 of 3 RCTs found benefit comparable to other exercise interventions	3 Low	Consistent	Direct	Precise	Low for improvement in long-term pain (or comparable improvement with other exercise interventions)
Long-term function	2 RCTs	No between group differences in WOMAC function vs. other exercise programs	Moderate-Low	Consistent		Precise	Low for improvement in long-term function (or comparable improvement with other exercise interventions)
Long-term other	1 RCT	Total WOMAC showed no difference vs. standard exercise	Low	N/A			Insufficient evidence
Aerobic Exercise							
Short-term pain, function, other outcomes	0 RCTs						Insufficient evidence
Medium-term pain, function, other outcomes	2 RCTs	No benefit for pain, function	Low-moderate				Insufficient evidence
Long-term pain	2 RCTs	No significant between-group differences in WOMAC pain vs. educational, passive	Moderate-high				Insufficient evidence

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		controls					
Long-term function	3 RCTs	No significant between-group differences in WOMAC function vs. educational control	2 Moderate, 1high	Consistent	Direct	NA	Low SoE for no beneficial effect on long-term function
Long-term other	1 RCT	No significant between-group differences in WOMAC total scores, SF-36 functional domain scores, TUG scores, or 6-minute walk distances vs. educational control	4/10	NA	Direct	NA	Insufficient evidence
General exercise therapy							
Short-term pain and function	1 RCT	No effect on pain or function	Low	NA	Direct	NA	Insufficient evidence
Short-term other outcomes	2 RCTs	No effects on WOMAC total, SF-36 TUG, or 6'-walk	Low	NA	Direct	NA	Low SoE for no short-term effect on other outcomes
Medium-term pain	2 RCTs	KOOS, P4, and WOMAC pain scores significantly improved over non-exercise control scores	Low	NA	Direct	Precise	Low SoE for benefit on medium-term pain
Medium-term function	2 RCTs	Significant improvement in KOOS and WOMAC function scores over non-exercise controls	Low	NA	Direct	Precise	Low SoE for benefit on medium-term function
Medium-term other outcomes	1 RCT	Inconsistent effects on other functions	Low	NA	Direct	Precise	Insufficient evidence
Long-term pain	4 RCTs	Improvement in VAS and WOMAC pain in	Moderate, 3 Low	Inconsistent	Direct	Precise	Low SoE for benefit on long-term pain

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		3 of 4 RCTs but no effect in 4th RCT					
Long-term function	2 RCTs	Inconsistent effects of exercise	2 Low	N/A	Direct	Precise	Low SoE for long-term benefit on function
Long-term other	4 RCTs	Inconsistent effects on 6"-walk, SF-36, but significant difference in WOMAC total, TUG	3 Low	Inconsistent	Direct	NA	Low SoE for long-term benefit on other outcomes
Tai Chi							
Short-term pain	3 RCTs	No between-group differences in WOMAC pain vs. resistance training, TAU, or education		Consistent	Direct	Precise	Low for a beneficial effect on short-term pain
Short-term function	3 RCTs			Inconsistent	Direct	Precise	Low SoE for beneficial effect on short-term function
Short-term other	1 RCT	Inconsistent differences between Tai chi and TAU	moderate	N/A	Direct	Precise	Insufficient evidence
Medium pain	2 RCTs	Significant between-group differences in WOMAC pain vs. education		N/A	Direct		Low SoE for beneficial medium-term effect on pain
Medium function	2 RCTs	Significant between-group difference in WOMAC function (MD -5.52, 95% CI -9.70, -1.34)		N/A			Low SoE for beneficial medium term effect on function
Long term pain, function, or other	0 RCTs						Insufficient evidence
Yoga							
Short-term pain	1 RCT	Significant between-group difference in WOMAC pain vs.	7/10	N/A	Direct	Precise	Insufficient evidence

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		waitlist control					
Short-term function	1 RCT	No significant between-group differences in WOMAC function	7/10	N/A			Insufficient evidence
Medium-term pain or function	0 RCTs						Insufficient evidence
Long-term pain or function	0 RCTs						Insufficient evidence
Ultrasound/heat/ infrared							
Heat and infrared	3 RCTs						Insufficient evidence
Ultrasound							
Short-term pain	3 RCTs						Low SoE for a short-term benefit on pain
Short-term function	1 RCT						Insufficient evidence
Short-term other	2 RCTs						Insufficient evidence
Medium and long-term outcomes							Insufficient evidence
Balneotherapy and Mud Therapy							
Balneotherapy							
Short-term outcomes	0 RCTs						Insufficient evidence
Medium-term pain	2 RCTs			Inconsistent			Inconsistent beneficial effect on medium-term pain (low SoE)
Medium-term function	2 RCTs		6,7/10	Consistent	Direct	Precise	Low SoE for beneficial effect on medium-term function
Medium-term other	2 RCTs		6,7/10	Consistent for QoL			Insufficient evidence
Long-term outcomes	0 RCTs						Insufficient evidence
Mud baths							
All outocmes	1 RCT	No between group differences in WOMAC pain for	4/10				Insufficient evidence

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		mud pack vs. placebo					
Topical mud therapy							
All outcomes	1 RCT	No between group differences in WOMAC function for mud pack vs. placebo	4/10				Insufficient evidence
Manual Therapy							
Short-term pain	7 RCTs (n=137 in pooled analysis of 3 RCTs)	No significant effect of manual therapy (administered by a therapist or by patients themselves) on short-term WOMAC pain **(SMD -0.57, 95% CI -1.60, 0.45) (n=244)**	4,6,7/10	Inconsistent	Direct	Precise	Low SoE for no effect of manual therapy on short-term pain
Short-term function	4 RCTs	No consistent benefit of any manual therapy compared with exercise or TAU		Inconsistent	Direct	Precise	Low SoE for no effect of manual therapy on short-term function
Short-term other	4 RCTs	No significant between-group differences in WOMAC total scores reported in 3 RCTs and in two treatment arms of the 4th RCT but significant effects in the two remaining arms	4, 6, 7, 8/10	Inconsistent	Direct	Precise	Low SoE for no short-term effect of manual therapy on WOMAC total
Medium-term outcomes	4 RCTs	Not possible to compare interventions across trials	3, 4, 7, 8/10	Inconsistent	Direct	N/R	Insufficient evidence
Medium-term other	3 RCTs		3, 4, 7/10	Inconsistent	Direct	N/R	Insufficient evidence for no effect of manual therapy on other medium term

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
							outcomes
Long-term pain	2 RCTs	Significant between group difference vs. exercise alone (MD -2.30, 95% CI -4.07, -0.53)	7/10	N/A	Direct	Precise	Low SoE for a beneficial effect of manual therapy on long-term pain
Pulsed Electromagnetic Field							
Short-term Pain	3 RCTs (n=94 in pooled analysis_	Non-statistically significant effect on VAS pain (SMD −12.44, 95% CI −34.41, 9.54)	1 moderate, 2 low	Inconsistent	Direct	Precise	Low SoE for an effect on short-term pain
Short-term function and other outcomes	1 RCT						Insufficient evidence
Medium-term outcomes	0 RCTs						Insufficient evidence
Long-term outcomes	0 RCTs						Insufficient evidence
Transcutaneous Electrical Nerve Stimulation (TENS)							
Short-term pain	4 RCTs (n=349)	Significant between-group difference on WOMAC pain vs. sham control 6 (**Pooled SMD -0.31, 95% CI -0.56, -0.06**) (n=343)	1 moderate, 1 unclear, 2 low	Inconsistent	Direct	Precise	Moderate for short-term effect of TENS on pain
Short-term function	3 RCTs	No between-group differences in WOMAC function but a higher % of TENS recipients had MCII than sham recipients in one study	1 Unclear, 2 low	Consistent	Direct	Precise	Low SoE for no beneficial effect on short-term function
Short-term other outcomes	2 RCTs	No between group difference in WOMAC total	1 unclear, 1 low	Consistent	Direct	Precise	Insufficient evidence
Medium-term pain	2 RCTs	No between-group differences in VAS or WOMAC pain	2 low	Consistent	Direct	Precise	Low for no effect of TENS on medium-term pain

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
Medium-term function	2 RCTs	No between-group differences in WOMAC function	2 low	Consistent	Direct	Precise	Low for no effect of TENS on medium-term function
Medium-term other outcomes	1 RCT	No between-group difference in WOMAC total	Low	N/A	Direct	Precise	Insufficient evidence
Long-term outcomes	0 RCTs						Insufficient evidence
Neuromuscular Electrical Stimulation (NMES)							
Short-term pain	4 RCTs	Significant between-group differences in 2 of 4 RCTs with no difference in 2 others	2 moderate, 2 low	Inconsistent	Direct	Precise	Low SoE for no beneficial effect of NMES on short-term pain
Short-term function	3 RCTs	2 RCTs showed no between-group differences in WOMAC function; 1 RCT showed significant between-group differences in Lequesne scores	1 moderate, 2 low	Inconsistent	Direct	Precise	Low SoE for no beneficial effect of NMES on short-term function
Medium-term pain	2 RCTs	No between group differences in one RCT, but persistent differences in 2nd RCT	2 moderate	Inconsistent	Direct	Precise	Insufficient evidence
Medium-term function	1 RCT	No between-group differences in WOMAC function	Moderate	N/A	Direct	Precise	Insufficient evidence
Long-term outcomes	0 RCTs						Insufficient evidence
Whole-body Vibration(WBV) left off here							
Short-term pain	3 RCTs	Inconsistent beneficial effects of WBV plus exercise (together or sequentially) compared with exercise alone	Low, high, unclear	Inconsistent	Direct	Precise	Low SoE for beneficial short-term effect

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
Short-term function	1 RCT	No significant between-group difference in WOMAC function for WBV plus strength training vs. strength training alone	low	N/A	Direct	Precise	Insufficient evidence
Short-term other	2 RCTs	No between-group differences in WOMAC total for WBV plus home exercise vs. home exercise alone; no differences in 6-minute walk distance, TUG, or SF-36	Low, high, unclear	N/A	Direct	Precise	Insufficient evidence
Medium-term pain	4 RCTs (n=193 in pooled analysis)	Pooled analysis showed no significant between-group difference in WOMAC pain (SMD −0.20, 95% CI −1.12, 0.71	2 low, moderate, unclear	Inconsistent	Direct	Precise	Low SoE for no medium-term effect of WBV on pain
Medium-term function	4 RCTs	Pooled analysis showed a small but significant between-group difference in WOMAC function (SMD −0.26, 95% CI −0.45, −0.06)(n=193)	2 low, moderate, unclear	Inconsistent	Direct	Precise	Low SoE for a beneficial effect of WBV on medium-term function
Medium-term other outcomes	4 RCTs (n=204 in pooled analysis)	No significant pooled between-group difference in 6-minute walk distances (SMD −31.17, 95% CI −82.60, 20.26)	2 low, moderate, unclear	Inconsistent	Direct	Imprecise	Low SoE for a medium-term effect on walking speed
	4 RCTs	No consistent	2 low, moderate,	Inconsistent	Direct	Precise	Insufficient evidence

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		between-group differences in WOMAC total, WOMAC stiffness, TUG	unclear				
Long-term outcomes	0 RCTs						Insufficient evidence
Orthoses	[left off here]						
Braces							
Short-term pain	1 RCT	Significant between-group difference in VAS pain (0-10 cm MD −1.30, 95% CI −2.01, −0.59)	Moderate	N/A	Direct	Precise	Insufficient evidence
Short-term function and other outcomes	0 RCTs						Insufficient evidence
Medium-term pain	1 RCT	Significant between group difference in VAS pain (0-10cm MD -2.30, no variance reported)	Unclear	N/A	Direct	N/R	Insufficient evidence
Medium-term function and other outcomes	0 RCTs						Insufficient evidence
Long-term pain	1 RCT	Significant between-group differences in VAS pain (0-10cm, MD −2.80, 95% CI −3.58, −2.02)	Unclear	N/A	Direct	Precise	Insufficient evidence
Long-term function and other outcomes	0 RCTs						Insufficient evidence
Shoe inserts							
Short-term pain	4 RCTs	3 of 4 RCTs showed significant between-group differences in at least one measure of VAS pain (no pooling possible); 1 of 2 RCTs showed a	1 low, 2 moderate, 1 unclear	Inconsistent	Direct	Precise	Low SoE for no beneficial effect on short-term pain

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		significant between-group difference in WOMAC pain					
Short-term function	3 RCTs	1 of 3 RCTs showed significant between-group differences in function; one that showed no difference did report MCII in 100% of insole users.	Low, moderate, unclear	Inconsistent	Direct	Precise	Low SoE for no beneficial effect on short-term function
Short-term WOMAC total	3 RCTs (n=125 in pooled analysis)	Pooled outcomes of 3 RCTs showed no significant between group difference in WOMAC total (SMD −0.37, 95% CI −1.26, 0.53)	Low, moderate, unclear	Inconsistent	Direct	Precise	Low SoE for no effect of orthotics on short-term overall improvement
Medium-term pain	3 RCTs (n=131 in pooled analysis)	Pooled outcomes of 3 RCTs showed no significant between group difference in WOMAC (SMD -0.4, 95% CI −1.35, 0.56)	1 low, 2 unclear	Inconsistent	Direct	Precise	Low SoE for no effect on medium-term pain
Medium-term function	4 RCTs	3 of 4 RCTs reported no between-group differences in function (2 Lequesne, 1 WOMAC) and 1 reported a significant between-group difference in WOMAC function (MD −10.06, 95% CI −19.68, −0.44)	1 low, 1 moderate, 2 unclear	Inconsistent	Direct	Precise	Low SoE for no beneficial effect on medium-term function
Long-term pain	2 RCTs	1 RCT found no between-group differences in WOMAC pain and 1 RCT found a	Low, unclear	Inconsistent	Direct	Precise	Insufficient evidence

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		significant difference in VAS pain					
Long-term function	2 RCTs	No between-group differences in Lequesne (1 RCT) or WOMAC (1 RCT) function	Low, moderate	Consistent	Direct	Precise	Insufficient evidence
Long term other	0 RCTs						Insufficient evidence
Custom Shoes	5 RCTs						
Short-term pain, function, other outcomes	0 RCTs						Insufficient evidence
Medium-term pain	2 RCTs	1 RCT reported a significant between group difference, and another RCT reported no significant difference in WOMAC pain scores	Low, unclear	Inconsistent	Direct	N/R	Insufficient evidence
Medium-term function	1 RCT	Significant between-group difference reported in WOMAC and Lequesne function scores	Low	Consistent	Direct	N/R	Insufficient evidence
Medium-term other	2 RCTs	No significant between-group differences in WOMAC total or walking distance	Moderate, low	Consistent	Direct	Imprecise	Insufficient evidence
Long-term pain	1 RCT	No significant between-group difference in WOMAC pain	Low	N/A	Direct	N/R	Insufficient evidence
Long-term function and other outcomes	0 RCTs						Insufficient evidence
Cane							
Short-term outcomes	1 RCT	Significant between-	Low	N/A	Direct	Precise	Insufficient evidence

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		group differences in pain and function					
Medium- and long-term outcomes	0 RCTs						Insufficient evidence
Weight-loss							
Short-term pain	1 RCT and 1 single-arm trial						Insufficient evidence for short-term effect of weight loss on pain
	1 RCT	Significant improvement in VAS pain with weight loss across 3 intervention arms (diet+ exercise, exercise, and diet only) but not proportional to actual weight loss	High	Inconsistent	Direct	Precise	
	1 single-arm trial	Significant improvement in KOOS pain with weight loss (MD 5, 95% CI 0.3, 9.7)	Not assessed	N/A	Direct	Precise	
Short-term function	1 RCT	Significant improvement in WOMAC function, Lequesne function, and proportion of individuals with improvements in function with weight loss in all treatment groups	High	Inconsistent	Direct	Precise	Insufficient evidence
Short-term other outcomes	1 single-arm trial	Significant improvement in TUG (seconds: MD−1.4, 95% CI−3.0 to −0.4) and 6-minute walk	Not assessed	Consistent	Direct	Precise	Insufficient evidence

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		from baseline with weight loss					
Medium-term pain	2 RCTs, 4 single-arm trials			Inconsistent	Direct	Precise	Moderate evidence for a medium-term effect of weight loss on pain
	2 RCTs	Significant between-group difference in WOMAC pain for weight loss vs. no weight loss in 1 RCT, but weight loss associated with decreased pain in only 1 of two treatment arms in 2nd RCT vs. control	Moderate, high	Inconsistent	Direct	Precise	
	Single-arm trials	1 single arm trial found significant decreases in pain with weight loss, and 3 (including CAROT, n=3,000) showed a significant dose-response relationship of weight loss with decreased pain	Not assessed	Consistent	Direct	Precise	
Medium-term function	3 RCTs, 3 single-arm trials						Low SoE for an effect of weight loss on medium term function
	RCTs	Weight loss significantly associated with between-group differences in WOMAC function in 2 of 3 RCTs	High, moderate	Inconsistent	Direct	Precise	

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
	3 single-arm trials	Weight loss significantly associated with WOMAC and KOOS function; dose-response relationship of weight loss and KOOS function	Not rated	Consistent	Direct	Precise	
Medium-term other outcomes							Insufficient evidence
	2 RCTs	Significant between-group differences in WOMAC total function (MD -10.70, 95% CI -17.01, -4.39) and 6-minute walk distance (MD -51.00, 95% CI -96.03, -5.97)	2 moderate	N/A	Direct	Precise	Insufficient evidence
	3 single-arm trials	Significant associations of weight loss with improvements in WOMAC stiffness, and TUG and significant dose-response association with SF-12 physical domain	Not rated				
Long-term pain	3 RCTs and 1 single-arm trial						Low SoE for effect of weight loss on long-term pain
	3 RCTs	1 RCT showed a significant between-group difference in WOMAC pain with weight loss (, MD -7.20, 95% CI -13.30, -1.10); 1 RCT showed	3 moderate	Inconsistent	Direct	Precise	

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		a non-significant between-group difference in WOMAC pain (between group differences in weight loss were small); and 1 RCT showed continued relationship between weight loss and decreased pain					
	1 single-arm trial	Ongoing trial shows improvement in VAS and WOMAC pain at 1 year	Not rated	N/A	Direct	Precise	
Long-term function	2 RCTs	1 RCT reported no between-group differences in WOMAC function; 1 RCT reported between-group differences WOMAC function by weight loss	2 moderate	Inconsistent	Direct	Precise	Insufficient evidence for a long-term effect of weight loss on function
Long-term other outcomes	2 RCTs	1 RCT reported no difference in WOMAC total scores; 1 RCT reported significant between group differences in 6-minute walk distance (MD −12.00, 95% CI −33.93, −9.93) and SF-36 physical domain scores (MD −2.70, 95% CI −4.89, −0.51)	2 moderate	Inconsistent	Direct	Imprecise for 6-minute walk	Insufficient evidence
Home-based and Self-Management							

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
Short-term pain	2 RCTs						Low SoE for short-term benefit for pain
	1 RCT home-based	1 RCT reported significant between-group differences in WOMAC pain for 3 home-based interventions vs. a sham-control: Strength training alone: MD −3.75, 95% CI −6.39, −1.11; agility training alone: MD −3.13, 95% CI −5.86, −0.40; strength+agility training: MD −3.00, 95% CI −5,45, −0.55	Moderate	Consistent	Direct	Precise	
	1 RCT self-management	Significant between-group difference in WOMAC pain scores (MD -1.50, 95% CI -2.33, -0.67) and the likelihood of achieving MCII (RR 0.20, 95% CI 0.08, 0.49)	Low	Consistent	Direct	Precise	
Short-term function	2 RCTs						Insufficient evidence
	1 RCT home-based	Significant between-group differences in WOMAC function for combined strength+agility training (MD -11.98, 95% CI -19.15, -4.81) and strength-training (MD -9.62, 95% CI -	Moderate	Inconsistent	Direct	Precise	

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		19.04, -0.20) vs. controls but not agility alone					
	1 RCT self-management	Significant between-group difference in WOMAC function (MD -5.30, 95% CI -7.24, -3.36); % achieving MCII was significantly different (RR 0.24, 99% CI 0.11, 0.51)	Low	N/A	Direct	Precise	
Short-term other outcomes	2 RCTs		Moderate, low				Insufficient evidence
Medium-term pain	3 RCTs self-management	1 RCT found significant between-group differences in VAS pain with pain coping skills training (PCST)+strength training vs. strength training alone (0-100: MD -8.20, 95% CI -15.32, -1.08) but not WOMAC pain; an RCT that combined PCST with behavioral weight management (BWM) found a significant between-group difference in WOMAC pain for BWM+PCST vs. BWM alone	Moderate, 2 low	Inconsistent	Direct	Precise	Low SoE for an effect of self-management on medium-term pain
Medium-term function	4 RCTs self-management	3 RCTs reported significant between group differences in WOMAC function	2 moderate, 2 low	Inconsistent	Direct	Precise	Low SoE for medium-term effect of self-management on function

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		(ST+PCST vs. ST alone: 0-68 points, MD -3.80, 95% CI -7.06, -0.54; BWM+PCST vs. standard care: 0-100 points, MD-12.40, 95% CI -17.29, -7.51; self-management vs. wait list: MD-3.50, 95% CI -6.14, -0.86); a 4th RCT found no effects					
Medium-term other outcomes	3 RCTs	1 RCT found significant between-group differences in WOMAC total (MD -4.10, 95% CI -7.43, -0.77); Significant between-group differences in TUG (MD -1.00, 95% CI -1.55, -0.45) and SF-36 (MD -5.70, 95% CI -10.97, -0.43) in 1 RCT but not another	Low	N/A	Direct	Precise	Insufficient evidence
Long-term outcomes	1 RCT	No between-group difference in WOMAC pain, function vs. control; significant improvement in Australian Q-6D	Low				Insufficient evidence
Key Question 2 Adverse Events							
Non-serious adverse events	56RCTs, 1 single arm trial	No systematic findings of non-serious AEs by intervention type, with the exception of	McHarms scores low (high RoB) for all studies	Inconsistent	Direct	N/A	Low SoE for a lack of systematic non-serious AEs among interventions

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings	Study limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	GRADE of evidence
		minor GI complaints among individuals following low-calorie diets					
Serious adverse events	18 RCTs	No systematic findings of SAEs by intervention type	McHarms scores low for all studies. Only 1 study that reported "no SAEs" defined SAEs	Inconsistent	Direct	N/A	Low SoE for a lack of systematic serious AEs among interventions

Abbreviations: BWM=behavioral weight management; CI=confidence intervals; MCID=minimum clinically important difference; MCII=minimum clinically important improvement; MD=mean difference; N/A=not applicable; NMES=neuromuscular electrical stimulation; N/R=not reported; NRS=Numeric Rating Scale; PCST=pain coping skills training; QoL=quality of life; RCT=randomized controlled trial; RoB=risk of bias; SF=short form; SMD=standardized mean difference; ST=strength training; TENS=transcutaneous electrical nerve stimulation; TUG=timed up and go; VAS=visual analog scale; WBV=whole-body vibration; WOMAC=Western Ontario McMaster Osteoarthritis Index

Appendix F. Quality of Included Studies

Table F1. Quality assessment of randomized controlled trials

Table F2. Quality assessment of studies reporting harms

Table F1. Quality assessment of randomized controlled trials (N=107 studies)

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants or Healthcare Provider Adequately Blinded	Outcome Assessors Blinded	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Incomplete Adherence/Compliance with Interventions Across Groups	Additional bias: Report power calculation/achieve adequate n	Overall Risk of Bias
Abbott JH, et al, 2015[65]	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	No	Moderate
Acosta-Olivo C, et al, 2014[26]	Low risk	Unclear	High risk	High risk	Unclear	Unclear	Unclear	Unclear	Low risk	No	Unclear
Atamaz FC, et al, 2012[87]	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Yes	Low risk	Low risk	Yes	Low
Atkins DV, et al, 2013[122]	Unclear	Unclear	High risk	High risk	Low risk	Unclear	No	Low risk	Unclear	Yes	Unclear
Avelar NC, et al, 2011[93]	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear	No	High risk	Low risk	Yes	Unclear
Azlin MNN, et al, 2011[116]	Unclear	Unclear	High risk	High risk	High risk	Unclear	No	High risk	Low risk	No	High
Bagnato GL, et al, 2016[92]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Barduzzi GO, et al, 2013[59]	Low risk	Low risk	High risk	Unclear	High risk	Unclear	Unclear	Unclear	Low risk	No	Unclear
Bartels EM, et al, 2014[68]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bellare N, et al, 2014[30]	Unclear	Unclear	High risk	Unclear	Low risk	Unclear	Unclear	Low risk	Low risk	No	Unclear
Bennell KL, et al, 2011[109]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Yes	Low risk	High risk	Yes	Low
Bennell KL, et al, 2015[53]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Bliddal H, et al, 2011[126]	Low risk	Low risk	Low risk	Low risk	High risk	Unclear	Unclear	Low risk	Low risk	Yes	Moderate
Bokaeian HR, et al, 2016[99]	Unclear	Low risk	High risk	Low risk	Low risk	Low risk	No	Low risk	Unclear	No	Low
Brosseau L, et al, 2012[39]	Low risk	Low risk	High risk	Low risk	High risk	Unclear	Unclear	Low risk	High risk	No	High
Bruce-Brand RA, et al, 2012[44]	Low risk	Unclear	High risk	Low risk	High risk	Low risk	No	Low risk	Low risk	No	Moderate

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants or Healthcare Provider Adequately Blinded	Outcome Assessors Blinded	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Incomplete Adherence/Compliance with Interventions Across Groups	Additional bias: Report power calculation/achieve adequate n	Overall Risk of Bias
Bruyere O, et al, 2008[33]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Yes	Low risk	Low risk	Yes	Low
Cakir S, et al, 2014[79]	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	Yes	Moderate
Callaghan MJ, et al, 2015[100]	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Yes	Low risk	Unclear	Yes	Moderate
Campos GC, et al, 2015[106]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Yes	Low risk	Unclear	Yes	Low
Carlos KP, et al, 2012[80]	Unclear	Unclear	High risk	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear	No	Unclear
Cheawthamai K, et al, 2014[117]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	No	Low risk	Unclear	No	Moderate
Chenchen, et al, 2016[70]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Cherian JJ, et al, 2015[101]	Unclear	Unclear	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear	Yes	Unclear
Cheung C, et al, 2014[71]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Yes	High risk	High risk	No	Moderate
Christensen R, et al, 2015[62]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Claes BEA, et al, 2015[130]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Coleman S, et al, 2012[133]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Yes	Low risk	Unclear	Yes	Low
Cortes Godoy V, et al, 2014[118]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Yes	Low risk	Low risk	No	Low
da Silva FS, et al, 2015[58]	Low risk	Low risk	High risk	Low risk	High risk	Low risk	No	Low risk	Unclear	No	Moderate
de Rooij M, et al, 2016[66]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Dundar U, et al, 2015[91]	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	No	Moderate
Dwyer L, et al,	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Yes	High risk	Unclear	Yes	Moderate

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants or Healthcare Provider Adequately Blinded	Outcome Assessors Blinded	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Incomplete Adherence/Compliance with Interventions Across Groups	Additional bias: Report power calculation/achieve adequate n	Overall Risk of Bias
2015[120]											
Elboim-Gabyzon M, et al, 2013[85]	Unclear	Low risk	High risk	High risk	Low risk	Unclear	No	Low risk	Low risk	Yes	Moderate
Erhart JC, et al, 2010[113]	Low risk	Unclear	Low risk	Low risk	High risk	Unclear	No	Low risk	Low risk	Yes	Moderate
Erhart-Hledik JC, et al, 2012[114]	Low risk	Low risk	Low risk	Low risk	High risk	Unclear	Yes	Low risk	Low risk	Yes	Low
Fioravanti A, et al, 2012[72]	Low risk	Unclear	High risk	Low risk	Low risk	Unclear	Yes	Unclear	Low risk	Yes	Moderate
Fioravanti A, et al, 2015[75]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Yes	Unclear	Low risk	Yes	Moderate
Fitzgerald GK, et al, 2011[55]	Low risk	Low risk	High risk	Low risk	High risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Fitzgerald GK, et al, 2016[67]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Foroughi N, et al, 2011[52]	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	No	Low risk	Low risk	Yes	Low
Fransen M, et al, 2014[31]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Ghroubi S, et al, 2008[123]	Unclear	Unclear	High risk	Unclear	Low risk	Unclear	Unclear	Low risk	Unclear	No	Unclear
Gormeli G, et al, 2015[24]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	No	Low risk	Low risk	Yes	Low
Gschiel B, et al, 2010[86]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear	No	Moderate
Hatef MR, et al, 2014[105]	Unclear	Unclear	Low risk	Low risk	High risk	Unclear	No	Low risk	Low risk	No	Moderate
Henriksen M, et al. 2014[56]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Herrero-Beaumont, et al, 2016[32]	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Hochberg MC, et al, 2008[134]	Unclear	Unclear	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Unclear	No	Unclear

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants or Healthcare Provider Adequately Blinded	Outcome Assessors Blinded	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Incomplete Adherence/Compliance with Interventions Across Groups	Additional bias: Report power calculation/achieve adequate n	Overall Risk of Bias
Hochberg MC, et al, 2015[29]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	Low risk	Unclear	Yes	Low
Hsieh RL, et al, 2012[78]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Yes	Low risk	Low risk	Yes	Low
Imoto AM, et al, 2012[48]	Unclear	Unclear	High risk	Low risk	Low risk	Unclear	Yes	Low risk	Low risk	Yes	Moderate
Imoto AM, et al, 2013[84]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Yes	High risk	Low risk	Yes	Low
Inal EE, et al, 2016[89]	Low risk	Low risk	Unclear	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear	No	Unclear
Inoshi Atukorala, et al, 2016[128]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Jones A, et al, 2012[115]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Jorge RTB, et al, 2015[49]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Yes	Low risk	Low risk	No	Low
Ju SB, et al, 2015[57]	Unclear	Unclear	High risk	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	No	Unclear
Kahan A, et al, 2009[38]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Yes	Low risk	Low risk	Yes	Low
Kapci Yildiz S, et al, 2015[81]	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear	No	High risk	Unclear	No	Low
Knoop J, et al, 2013[61]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Koca B, et al, 2009[104]	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear	Low risk	Unclear	No	Unclear
Koli J, et al, 2015[41]	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Yes	Low risk	High risk	Yes	Low
Kulisch A, et al, 2014[73]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Yes	Unclear	Low risk	Yes	Moderate
Laufer Y, et al, 2014[82]	Unclear	Low risk	Low risk	High risk	Low risk	Low risk	No	Low risk	Low risk	No	Moderate
Lim JY, et al, 2010[63]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Yes	Low risk	Low risk	Yes	Low
Mahboob N, et al,	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear	Yes	Unclear	Unclear	No	Unclear

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants or Healthcare Provider Adequately Blinded	Outcome Assessors Blinded	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Incomplete Adherence/Compliance with Interventions Across Groups	Additional bias: Report power calculation/achieve adequate n	Overall Risk of Bias
2009[74]											
Makovey J, et al, 2015[129]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Messier SP, et al, 2013[125]	Unclear	Unclear	High risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	Yes	Moderate
Miller GD, et al, 2006[124]	Unclear	Unclear	High risk	High risk	Low risk	Unclear	No	Low risk	Low risk	No	Moderate
Mizusaki Imoto A, et al, 2013[83]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Nam CW, et al, 2014[51]	Unclear	Unclear	High risk	Unclear	Low risk	Unclear	Yes	Low risk	Low risk	No	Moderate
Nelson FR, et al, 2013[90]	Low risk	Low risk	Low risk	Low risk	High risk	Unclear	Yes	Low risk	Low risk	Yes	Low
Oliveira AM, et al, 2012[47]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Yes	Low risk	Low risk	Yes	Low
Palmer S, et al, 2014[88]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Park YG, et al, 2013[98]	Unclear	Unclear	High risk	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	No	Unclear
Patel S, et al, 2013[23]	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	No	High risk	Low risk	Yes	Moderate
Perlman AI, et al, 2012[121]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Yes	High risk	Low risk	No	Moderate
Rabini A, et al, 2015[94]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Yes	Low risk	Low risk	Yes	Low
Rayegani SM, et al, 2014[25]	Low risk	High risk	High risk	High risk	Low risk	Unclear	No	Unclear	Low risk	No	High
Richette P, et al, 2011[131]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No	N/A
Rodrigues PT, et al, 2008[103]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	No	Moderate
Rogers MW, et al, 2012[46]	Low risk	Unclear	Low risk	High risk	High risk	Low risk	Unclear	Low risk	Low risk	No	Moderate

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants or Healthcare Provider Adequately Blinded	Outcome Assessors Blinded	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Incomplete Adherence/Compliance with Interventions Across Groups	Additional bias: Report power calculation/achieve adequate n	Overall Risk of Bias
Rosedale R, et al, 2014[64]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Yes	Low risk	Unclear	Yes	Low
Salacinski AJ, et al, 2012[43]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Yes	High risk	High risk	Yes	Low
Samut G, et al, 2015[40]	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear	Low risk	Low risk	No	Unclear
Sattari S, et al, 2011[102]	Low risk	Unclear	High risk	High risk	Low risk	Unclear	Unclear	Low risk	Unclear	No	Unclear
Sawitzke AD, et al, 2010[28]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Schlenk EA, et al, 2011[42]	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	Yes	Low risk	Unclear	Yes	Low
Segal NA, et al, 2015[60]	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	No	Low risk	Low risk	Yes	Low
Simao AP, et al, 2012[97]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	No	High risk	Low risk	Yes	Moderate
Simental-Mendia M, et al, 2016[27]	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	No	Low risk	Low risk	Yes	Unclear
Singh S, et al, 2016[50]	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear	No	Low
Somers TJ, et al, 2012[127]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Yes	Unclear	Unclear	Yes	Moderate
Stambolova Ivanova MP, 2015[34]	Unclear	Unclear	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear
Stefanik J, et al, 2015[132]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Toda Y, et al, 2006[108]	High risk	High risk	Low risk	Low risk	Low risk	Unclear	No	Low risk	Unclear	No	Moderate
Trombini-Souza F, et al, 2013[111]	Unclear	Unclear	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear
Trombini-Souza F, et al, 2015[112]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Tsai PF, et al,	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear	Yes	Low risk	Unclear	No	Unclear

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants or Healthcare Provider Adequately Blinded	Outcome Assessors Blinded	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Incomplete Adherence/Compliance with Interventions Across Groups	Additional bias: Report power calculation/achieve adequate n	Overall Risk of Bias
2013[69]											
Wallace DA, 2006[107]	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear	Unclear	Unclear	No	Unclear
Wang P, et al, 2015[95]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Yes	Low risk	Low risk	Yes	Low
Wang P, et al, 2015[96]	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear	Yes	Low risk	Low risk	Yes	Low
Wortley M, et al, 2013[45]	Unclear	Unclear	High risk	Unclear	High risk	Unclear	No	High risk	Low risk	No	High
Yildirim N, et al, 2010[77]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Yes	Unclear
Zegels B, et al, 2013[37]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Yes	Low risk	Low risk	Yes	Low
Zhang Y, et al, 2012[119]	Low risk	Low risk	High risk	High risk	High risk	Unclear	Yes	Low risk	Unclear	No	Moderate

Table F2. Quality assessment of studies reporting harms (N=57)

Author, year	Were the harms predefined using standardized or precise definitions?	Was the mode of harms collected specified as active?	Was the potential occurrence of harmful events collected at pre-specified intervals?	Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	Was the TOTAL NUMBER of participants affected by harms specified for each study arm?	If the study reported that there were no serious AE's reported did they define serious AEs?
Abbott JH, et al, 2015[65]	No	Unclear	Unclear	Yes	Yes	Not applicable
Atamaz FC, et al, 2012[87]	Unclear	Unclear	Unclear	No	No	Not applicable
Bagnato GL, et al, 2016[92]	No	Unclear	Unclear	Yes	Yes	Not applicable
Bellare N, et al, 2014[30]	No	No	No	No	No	Not applicable
Bennell KL, et al, 2011[109]	No	Yes	Yes	Yes	Yes	Not applicable
Bennell KL, et al, 2015[53]	Yes	Yes	Unclear	Yes	Yes	Not applicable
Bliddal H, et al, 2011[126]	Unclear	Unclear	Unclear	No	No	Not applicable
Callaghan MJ, et al, 2015[100]	Unclear	Yes	Yes	Yes	Yes	Not applicable
Campos GC, et al, 2015[106]	Yes	Unclear	Unclear	Yes	Yes	Not applicable
Chenchen, et al, 2016[70]	Unclear	Yes	Yes	No	No	Yes
Cherian JJ, et al, 2015[101]	Yes	Unclear	Unclear	No	No	Yes
Cheung C, et al, 2014[71]	Unclear	Yes	Unclear	Yes	Yes	Not applicable
Christensen R, et al, 2015[62]	Yes	Yes	Yes	Yes	Yes	Not applicable
Coleman S, et al, 2012[133]	Unclear	Unclear	Unclear	Yes	Yes	Not applicable
Dwyer L, et al, 2015[120]	Yes	Unclear	Unclear	Yes	Yes	Not applicable
de Rooij M, et al, 2016[66]	No	Unclear	Unclear	No	No	No
Elboim-Gabyzon M, et al, 2013[85]	No	No	Unclear	Yes	Yes	Not applicable
Erhart JC, et al, 2010[113]	No	No	Unclear	No	No	Not applicable

Author, year	Were the harms predefined using standardized or precise definitions?	Was the mode of harms collected specified as active?	Was the potential occurrence of harmful events collected at pre-specified intervals?	Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	Was the TOTAL NUMBER of participants affected by harms specified for each study arm?	If the study reported that there were no serious AE's reported did they define serious AEs?
Fioravanti A, et al, 2015[75]	No	Unclear	Unclear	Yes	Yes	No
Fitzgerald GK, et al, 2011[55]	No	Unclear	Unclear	Yes	Yes	No
Fitzgerald GK, et al, 2016[67]	Unclear	Unclear	Unclear	Yes	Yes	Not applicable
Foroughi N, et al, 2011[52]	Yes	Yes	Yes	Yes	Yes	Not applicable
Fransen M, et al, 2014[31]	No	Yes	Yes	No	No	Not applicable
Ghroubi S, et al, 2008[123]	Unclear	No	No	Unclear	Unclear	Not applicable
Gschiel B, et al, 2010[86]	Unclear	Unclear	Unclear	Yes	Yes	Not applicable
Herrero-Beaumont, et al, 2016[32]	No	Unclear	Unclear	No	Yes	Not applicable
Hochberg MC, et al, 2008[134]	No	Unclear	Unclear	Yes	Yes	Not applicable
Hochberg MC, et al, 2015[29]	Yes	Unclear	Unclear	Yes	Yes	Not applicable
Hsieh RL, et al, 2012[78]	No	No	Unclear	Yes	Yes	Not applicable
Imoto AM, et al, 2012[48]	No	No	No	Yes	Yes	Not applicable
Imoto AM, et al, 2013[84]	No	Unclear	Unclear	Yes	Yes	Not applicable
Jorge RTB, et al, 2015[49]	Unclear	No	Unclear	Yes	Unclear	Not applicable
Kahan A, et al, 2009[38]	No	Unclear	Unclear	No	Yes	Not applicable
Kapci Yildiz S, et al, 2015[81]	Unclear	Unclear	Unclear	Yes	Yes	Not applicable
Knoop J, et al, 2013[61]	Yes	Unclear	Unclear	Yes	Yes	Yes
Koli J, et al, 2015[41]	Unclear	Unclear	Unclear	Yes	Yes	Not applicable
Laufer Y, et al, 2014[82]	No	No	No	Yes	Yes	Not applicable

Author, year	Were the harms predefined using standardized or precise definitions?	Was the mode of harms collected specified as active?	Was the potential occurrence of harmful events collected at pre-specified intervals?	Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	Was the TOTAL NUMBER of participants affected by harms specified for each study arm?	If the study reported that there were no serious AE's reported did they define serious AEs?
Lim JY, et al, 2010[63]	Unclear	Yes	Unclear	No	No	Not applicable
Messier SP, et al, 2013[125]	Unclear	Unclear	Unclear	Yes	Yes	Not applicable
Mizusaki Imoto A, et al, 2013[83]	No	Unclear	Unclear	Yes	Yes	Not applicable
Nelson FR, et al, 2013[90]	No	Unclear	Unclear	Yes	Yes	Not applicable
Oliveira AM, et al, 2012[47]	No	Unclear	Unclear	Yes	Yes	Not applicable
Park YG, et al, 2013[98]	No	Unclear	Unclear	Yes	Yes	Not applicable
Patel S, et al, 2013[23]	No	Unclear	Unclear	No	Yes	Not applicable
Perlman AI, et al, 2012[121]	No	Unclear	Unclear	Yes	Yes	Not applicable
Rabini A, et al, 2015[94]	Unclear	Unclear	Unclear	Yes	Yes	Not applicable
Rayegani SM, et al, 2014[25]	No	Unclear	Unclear	Yes	Yes	Not applicable
Rodrigues PT, et al, 2008[103]	Unclear	Unclear	Unclear	Yes	Yes	Not applicable
Salacinski AJ, et al, 2012[43]	Unclear	Unclear	Unclear	Yes	Yes	Not applicable
Sawitzke AD, et al, 2010[28]	No	Yes	Yes	Yes	Unclear	Not applicable
Segal NA, et al, 2015[60]	No	Yes	Yes	Yes	Yes	Not applicable
Simental-Mendia M, et al, 2016[27]	No	No	Unclear	No	No	No
Somers TJ, et al, 2012[127]	Unclear	Unclear	Unclear	Yes	Yes	Not applicable
Wang P, et al, 2015[95]	Unclear	Yes	Yes	Yes	Yes	Not applicable
Wang P, et al, 2015[96]	No	No	Unclear	Yes	Yes	No
Zegels B, et al,	No	Unclear	Unclear	No	No	Not applicable

Author, year	Were the harms predefined using standardized or precise definitions?	Was the mode of harms collected specified as active?	Was the potential occurrence of harmful events collected at pre-specified intervals?	Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	Was the TOTAL NUMBER of participants affected by harms specified for each study arm?	If the study reported that there were no serious AE's reported did they define serious AEs?
2013[37]						
Zhang Y, et al, 2012[119]	Unclear	Unclear	Unclear	Yes	Yes	Not applicable

Appendix G. Policies, Guidelines, Coverage, and Stakeholder Information on Interventions of Interest

Table G1. Policies, guidelines, coverage, stakeholder information on interventions of interest

Intervention	Current Guidelines	FDA Approval for Indicated Use	CMS Coverage
Glucosamine Chondroitin	ACR: Conditional recommendation *against* use AAOS: Recommendation *against* use glucosamine and chondroitin (strong)	Evidence insufficient to demonstrate reduction in risk or disease modification (2004) Unclear regarding treatment of symptoms	Not relevant (over-the-counter)
Platelet Rich Plasma	ACR: not mentioned AAOS: *unable* to recommend *for or against* growth factor injections and/or platelet rich plasma (inconclusive)	Off-label use for an FDA-approved product	CMS National Coverage Determination: covered only for certain chronic non-healing wounds
Mesenchymal Stem Cells	ACR: not mentioned AAOS: not mentioned	Not approved by the FDA	Not covered for OA National Coverage Determination for Stem Cell Transplantation: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=45&ncdver=5&NCAId=9&IsPopup=y&bc=AAAAAAAAAgAAAA%3D%3D&
Weight loss	ACR: strongly recommends weight loss (for persons who are overweight) AAOS: suggests weight loss *for* patients with symptomatic osteoarthritis of the knee OAK and a BMI ≥ 25. (moderate)	Not searched	**Bariatric Surgery for the Treatment of Morbid Obesity** Certain procedures for the treatment of obesity are covered for Medicare beneficiaries who have a BMI ≥35, have at least one co-morbidity related to obesity and have been previously unsuccessful with the medical treatment of obesity. https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=57&ncdver=5&NCAId=258&NcaName=Bariatric+Surgery+for+the+Treatment+of+Morbid+Obesity&IsPopup=y&bc=AAAAAAAACAAAAA%3D%3D&. **Other Treatments for Obesity** **Nationally Noncovered Indications** 1. Treatments for obesity alone remain non-covered. 2. Supplemented fasting is not covered under the Medicare program as a general treatment for obesity, with certain exceptions. Where weight loss is necessary before surgery in order to ameliorate the complications posed by obesity when it coexists with pathological conditions such as cardiac and respiratory diseases,

Intervention	Current Guidelines	FDA Approval for Indicated Use	CMS Coverage
			diabetes, or hypertension (and other more conservative techniques to achieve this end are not regarded as appropriate), supplemented fasting with adequate monitoring of the patient is eligible for coverage on a case-by-case basis or pursuant to a local coverage determination. The risks associated with the achievement of rapid weight loss must be carefully balanced against the risk posed by the condition requiring surgical treatment
Physical therapy	ACR: conditionally recommends receiving manual therapy in combination with supervised exercise. AAOS: Not found specifically on physical therapy, although there were studies presented [unless if the following: "We are unable to recommend for or against the use of physical agents (including electrotherapeutic modalities) in patients with symptomatic osteoarthritis of the knee. (inconclusive)" "We are unable to recommend for or against manual therapy in patients with symptomatic osteoarthritis of the knee. (inconclusive)"]	Not relevant	Covered under Part B subject to certain conditions and limitations
TENS/NMES	ACR: conditionally recommends instruction in use of TENS AAOS: found insufficient evidence supporting use of TENS		Medicare Part B may cover a TENS unit for a patient who has been suffering from chronic pain for at least three months, for which other, standard pain relief methods have failed
Braces and/or orthotics (orthoses or wedges)	ACR: conditionally recommends using medially directed patellar taping; wearing medially wedged insoles if a patient with OAK has lateral compartment OA, wearing laterally wedged subtalar strapped insoles if a patient with OAK have medial compartment OA; has no recommendations on wearing laterally wedged insoles and wearing knee braces.	Unloader braces are approved by the FDA as medical equipment [need to check orthotics]	Medicare Part B covers medically necessary arm, leg, back, and neck braces under the durable medical equipment prefabricated **orthotics** benefit, subject to certain conditions and limitations. Shoes and foot orthotics are covered under certain circumstances only when criteria are met.

Intervention	Current Guidelines	FDA Approval for Indicated Use	CMS Coverage
	AAOS: cannot suggest that lateral wedge insoles be used for patients with symptomatic medial compartment osteoarthritis of the knee. (moderate)		

Appendix H. Adverse Events

Table H1. Adverse events by treatment (number (%))

Table H1a. Platelet-rich plasma (PRP)

Reference	Type	Control	PRP 1 injection	PRP 2 injections
Patel, 2013[23]	Pain and stiffness	0	6(22.22)	11(44.00)
	Adverse events (AEs)	0	4(14.8)	3(12)
Rayegani, 2014[25]	Significant Complications	0	0	
Simental-Mendia, 2016[27]	Major AEs	0	0	
	Pain	0	1(3.0)	0

Table H1b. Glucosamine/chondroitin

Reference	Type	Control	Glucosamine	Chondroitin	Glucosamine+ chondroitin	Celecoxib
Hochberg, 2008[134]	Death	0	0	0	0	0
	Non-fatal myocardial infarction (MI)	0	0	0	0	0
	GI bleed	0	0	0	0	0
	Cerebrovascular accident (CVA)	0	0	0	0	1 (0.31)
	Transient ischemic attack (TIA)	0	1(0.32)	0	0	1(0.31)
	Withdrawal (w/d) due to AE	11(3.52)	9(2.84)	20(6.29)	12(3.79)	7(2.20)
Kahan, 2009[38]	Good or very good tolerability	291(93)		290(94)		
	GI side effects	18(5.9)		19(6)		
	W/d due to AEs	17(5)		16(5)		
Sawitzke, 2010[28]	MI	0	1(0.75)	0	2(1.55)	0
	Coronary angioplasty	1(0.76)	0	0	0	0
	Hip arthroplasty	0	0	0	0	1(0.70)
	CVA	0	0	1(0.75)	0	2(1.41)
	Abdominal wall abscess	0	0	0	0	1
	Suicide	1(0.76)	0	0	0	0
	HTN	1(0.76)	0	0	1(0.78)	0
	Palpitations	0	0	0	1	0
	TIA	0	0	0	1	0
	Serious GI bleed	0	0	0	0	0
Fransen, 2014[31]	W/d due to AE	8(5.30)	8(5.26)	11(7.28)	7(4.6)	
	w/d due to blood glucose issues	1(0.66)	0	1(0.66)	0	
	W/d due to cardiac	1(0.66)	0	0	3(1.98)	
	W/d due to GI,	5(3.31)	4(2.63)	4(2.64)	2(1.32)	

Reference	Type	Control	Glucosamine	Chondroitin	Glucosamine+ chondroitin	Celecoxib
	rash					
		Diet alone			G/C+ diet	
Bellare, 2014[30]	SAE	0			0	
Hochberg, 2016[29]	AEs				22(7.24)	22(7.36)

Table H1c. Chondroitin

Reference	Type	Control	1200mg Chondroitin qd/400mg tid
Zegels, 2013[37]	Serious AE	2(1.7)	2(1.7)/4(3.41)
	AEs related to treatment	49(41)	31(26)/31(26)

Table H1d. Strength training

Reference	Type	Control	Exercise
Oliveira, 2012[47]	Exercise intolerance	0	2(4)
Foroughi, 2011[52]	Minor AEs	1(3.57)	0
Imoto, 2012[48]	Significant knee inflammation	0	2(4)
Jorge, 2015[49]	Knee pain	0	3(10.3)

Table H1e. Agility training

Reference	Type	Control	Exercise
Knoop, 2013[61]	Any serious AEs	0	0
Fitzgerald, 2011[55]	Serious AEs	0	0

Table H1f. Yoga

Reference		Control	Yoga
Cheung, 2014[71]	AEs	0	0

Table H1g. Manual therapy

Reference		Control	Exercise	Exercise + booster	Exercise + manual therapy	Exercise + booster+ manual therapy	Massage/ Acupressure
Abbott, 2015[65]	Hip pain		1(5.62)	0	0	0	
	Fall on knee associated with exercise		0	0	0	1(5.62)	
Zhang, 2012[119]	AEs	0					0
Perlman, 2012[121]	Any AEs	0					0(30-120-minutes per week
Dwyer,	Any AEs		0		0		0

Reference		Control	Exercise	Exercise + booster	Exercise + manual therapy	Exercise + booster+ manual therapy	Massage/ Acupressure
2015[120]							

Table H1h. Infrared (IR)

Reference		Control	IR
Hsieh, 2012[78]	AEs	0	0

Table H1i. Mud bath

Reference		Control	Mud bath
Fioravanti, 2015[75]	Mild hypotension	0	3(5.66)
	Febrile episode	0	1(1.89)
	Gastric pyrosis	3(6)	0
	Epigastralgia	2(4)	0

Table H1j. Braces

Reference		Control	Brace
Callaghan, 2015[100]	Bilateral leg swelling	0	1(1.59)
Cherian, 2015[101]	Severe AEs	0	0
	Minor irritation at pad placement sites	0	1(6.90)

Table H1k. Orthotics

Reference		Control	Insole
Bennell, 2011[109]	Back pain	1(1.03)	9(8.74)
	Foot pain	14(14.43)	32(31.07)
	Uncomfortable or difficulty fitting in shoes	4(4.12)	15(14.56)
	Increased knee pain	5(5.14)	2(1.94)
	Instability	1(1.03)	0
	Self-reported problems with insoles	21(21.65)	42(40.78)
Rodrigues, 2008[103]	Mild discomfort	1(7.14)	0
Campos, 2015[106]	Ankle pain	4(13.79)	5(17.24)

Table H1l. Minimalist shoe

Reference		Control	Shoe
Erhart, 2010[113]	Hip pain	1(2.56)	0
	Shoe discomfort	4(10.26)	1(2.5)
	Foot pain	2(5.13)	0
	Sciatic pain	0	1(2.5)

Reference		Control	Shoe
	Meniscectomy	2(5.2)	1(2.5)
	TKR	1(2.56)	0

Table H1m. TENS

Reference		Sham TENS	TENS
Atamaz, 2012[87]	Worsening of symptoms	3(8.11)	3(8.11)
Gschiel, 2010[86]	AEs	0	0

Table H1n. NMES

Reference		Sham NMES	NMES
Elboim-Gabyzon, 2013[85]	Pneumonia	1(3.03)	1(3.33)
Laufer, 2014[82]	Adverse reaction to treatment	0	0
Imoto, 2013[84]	Hypertensive crisis	0	1(2)
		Exercise	NMES + exercise
Mizusaki Imoto, 2013[83]	Blood pressure spike	0	1

Table H1o. Whole body vibration

Reference		Control	Treated
Rabini, 2015[94]	AEs	0	0
Wang, 2015[95]	AEs	0	0
Wang, 2015[96]	Slight low back pain	0	1(5.62)
	Severe AEs	0	0
Park, 2013[98]	Any AE	0	1(9.09)

Table H1p. Weight loss

Reference		Control	Exercise	Diet	Diet + exercise
Messier, 2013[125]	Heart palpitations		1	0	0
	ALS		0	0	1(0.66)
	Stroke		0	0	1(0.66)
	Lung HTN		0	0	1(0.66)
	Lung infection		0	0	1(0.66)
	Cancer		1(0.66)	1(0.67)	2(1.32)
	Staph infection		0	0	1(0.66)
Ghroubi, 2008[123]	Worsening knee pain	0	0	0	0
Christensen, 2015[62]	Nausea	1(1.56)	8(12.5)	3(4.69)	
	Diarrhea	4(6.2)	6(9.38)	3(4.69)	
	Constipation	8(12.5)	7(10.94)	9(14.06)	
	Flatulence	14(21.88)	10(15.63)	19(29.69)	
	Epigastric pain	1(1.56)	7(10.94)	6(9.38)	
	Vomiting	1(1.56)	4(6.25)	3(4.69)	

Reference		Control	Exercise	Diet	Diet + exercise
	Abdominal pain	3(4.69)	4(6.25)	6(9.38)	
	Heartburn	3(4.69)	9(14.06)	3(4.69)	
	Biliary symptoms	0	4(6.25)	2(3.13)	
	Cramps	8(12.5)	7(10.93)	6(9.38)	
	Joint pain	12(18.75)	12(18.75)	15(23.44)	
	Back pain	10(15.62)	6(9.38)	11(17.19)	
	Swollen joints	11(17.19)	10(15.63)	11(17.19)	
	Sciatic pain	9(14.06)	7(10.94)	4(6.25)	
	Dizziness	8(12.5)	10(15.63)	7(10.94)	
	Headache	5(7.81)	12(18.75)	6(9.38)	
	Anxiety	2(3.13)	5(7.81)	3(4.69)	
	Sleeplessness	11(17.18)	11(17.19)	6(9.38)	
	Fatigue	12(18.75)	13(20.31)	8(12.5)	
	Mood changes	5(7.81)	13(20.31)	5(7.81)	
	Depressive tendencies	4(6.25)	5(7.81)	6(9.38)	
	Dry skin	6(9.38)	6(9.38)	4(6.25)	
	Allergic rash	4(6.25)	7(10.94)	5(7.81)	
	Redness	2(3.13)	7(10.94)	4(6.25)	
	Eczema	3(4.69)	5(7.81)	4(6.25)	
	Perianal itching	2(3.13)	11(17.2)	5(7.81)	
	Skin irritation	3(4.69)	8(12.5)	5(7.81)	
	Urticaria	1(1.56)	3(4.69)	3(4.69)	
	Cold sensitivity	6(9.38)	8(12.5)	9(14.06)	
	Influenza	2(3.13)	5(7.8)	7(10.9)	
	Hair loss	2(3.13)	7(10.9)	5(7.8)	
	Bad breath	5(7.8)	9(14.06)	6(9.38)	
	Toothache	4(6.25)	6(9.38)	4(6.25)	
Bliddal, 2011[126]	Constipation			5(11.36)	
	Increased flatulence			4(9.09)	
	Dizziness			2(4.55)	
	Heightened cold sensitivity	0		2(4.55)	

Table H1q. Pain Coping Skills Training (PCST)

Reference	Type	Control	Exercise	PCST	PCST+ exercise	Weight manage-ment	PCST+ weight manage-ment
Bennell, 2015[53]	Number reporting AEs during treatment		28(37.33)	4(5.4)	24(37.3)		
	Number AEs during treatment		38(50.67)	7(9.46)	31(42.47)		
	Increased knee pain during treatment		22(29.33)	2(2.70)	15(20.55)		
	Pain in other regions		11(14.67)	3(5.05)	11(15.07)		

Reference	Type	Control	Exercise	PCST	PCST+ exercise	Weight manage-ment	PCST+ weight manage-ment
	during treatment						
	Swelling/ inflammation during treatment		2(2.67)	2(2.70)	2(2.74)		
	Increased stiffness during treatment		2(2.67)	0	3(4.11)		
	Knee instability during treatment		1(1.33)	0	0		
	Number participants reporting AEs during followup		12(16)	4(5.41)	7(9.59)		
	Number of AEs during followup		15(20)	4(5.41)	8(10.96)		
	Increased knee pain during followup		6(8)	4(5.41)	3(4.11)		
	Pain in other regions during follow-up		7(9.33)	0	2(2.74)		
	Swelling/ inflammation during followup		2(2.67)	0	2(2.74)		
	Increased stiffness during followup		0	0	1(1.37)		
Somers, 2012[127]	Fall from treadmill	0		0		0	1(1.61)

Table H1r. Self-management

Reference	Type	Control	Self-Management
Coleman, 2012[133]	Number with serious AEs	0	0

Table H1s. Aerobic training

Reference	Type	Control	Aerobic
Salacinski, 2012[43]	AEs	0	0

Table H1t. General exercise

Reference	Type	Control	Aerobic
de Rooij, 2016[66]	Serious AEs	0	0

Appendix I. MCID Cutoffs

Table I1. MCID cutoffs developed or used in a representative sample of articles

Author, Year	Condition/ Intervention /FU	Cutoffs	Notes
Eberle, 1999 PMID: 10489324	Knee OA HA injection, 6 month followup	VAS pain: 8.4mm on a 0-100 mm scale; 0.7 points on Lequesne 24-point scale	Anchor question: complaints reduced
Angst 2001 PMID:11501727	Knee or hip OA Rehabilitation, 3 month followup	WOMAC pain: 0.75 (0-10 scale) WOMAC function and total: 0.67 SF-36 physical function: 3.3 (0-100 scale)	Anchor question: current subjective health much better, slightly better, no change, slightly worse... Converted all 5 WOMAC pain item scores to a 0-10 scale and took the average) Separate values for worsening and improvement
Salaffi 2004 PMID: 15207508	Chronic musculoskeletal pain (OA knee, OA hip, AS, RA, OA hand) Not described	NRS: 15% or 1 point decrease for minimum improvement, 33% or 2 points for much better (which they regarded as clinical improvement)	Anchor: Patient global impression of change
Tubach 2005 PMID:15208174	Knee or hip OA NSAIDs, 4 weeks	Knee: VAS pain: −19.9mm (−40.8%) WOMAC function: −9.1(−26%)	WOMAC 17 items, 5-point likert scale, total score normalized to 0-100 scale MCII Initial severity affected MCII but age, disease duration, and sex did not
Wandel 2010 PMID: 20847017	Knee or hip OA Glucosamine-chondroitin vs. placebo network MA	MCID 0.37 SD units, corresponding to 0.9cm (0-10cm VAS scale)	Median pooled SD of 2.5cm used to back transform effect sizes to 10cm VAS scale
OMERACT-OARSI responder criteria Pham 2003 PMID: 12858473	Knee or hip OA	Clinical response was defined as either 1. improvement of at least 50% in pain or function and an absolute change of at least 20 points on a scale of 0-100 in the WOMAC pain or function subscores, or 2. at least 2 of the following criteria: improvement of at least 20% and an absolute change greater than 10 points on a scale of 0-100 in the WOMAC pain score, improvement of at least 20% and an absolute change greater than 10 points (on a 0-100 scale) in the WOMAC function score, or	WOMAC pain and function scales converted to single 0-100 scores.

		improvement of at least 20% in the patient Global Assessment score and an absolute change >10 points on a scale of 0-100	