Comparative Effectiveness Review
Number 190

Effective Health Care Program

Treatment of Osteoarthritis of the Knee: An Update Review

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

Purpose of Review

To assess the effectiveness of several treatments for osteoarthritis of the knee.

Key Messages

- Home-based exercise programs and tai chi show short- to medium-term benefits for symptoms (primarily pain, function, and quality of life) but lack data on long-term benefits.
- Strength and resistance training, pulsed electromagnetic field therapy, and transcutaneous electrical nerve stimulation show mostly short-term benefits, whereas agility training shows short- and long-term benefits.
- Weight loss and general exercise programs show medium- and long-term benefits.
- Intra-articular platelet-rich plasma, balneotherapy, and whole body vibration show medium-term benefits.
- Glucosamine-chondroitin and glucosamine or chondroitin sulfate alone show medium-term benefits with no long-term benefits for pain or function.

AHRQ Agency for Healthcare Research and Quality
Effective Health Care Program

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 therapie, 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

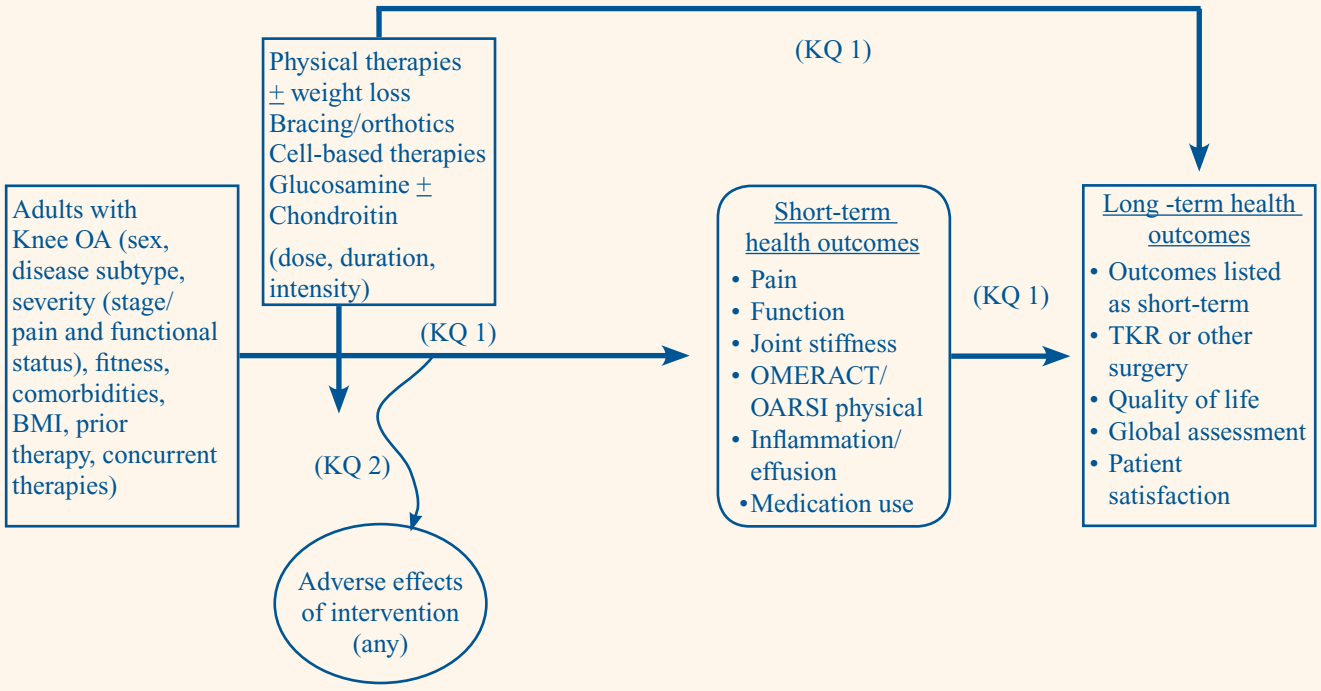

Figure notes: BMI = Body Mass Index; KQ = Key Question; OA = Osteoarthritis; OARSI = Osteoarthritis Research Society International; OMERACT = Outcome Measures in Rheumatology; TKR = Total Knee Replacement.

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

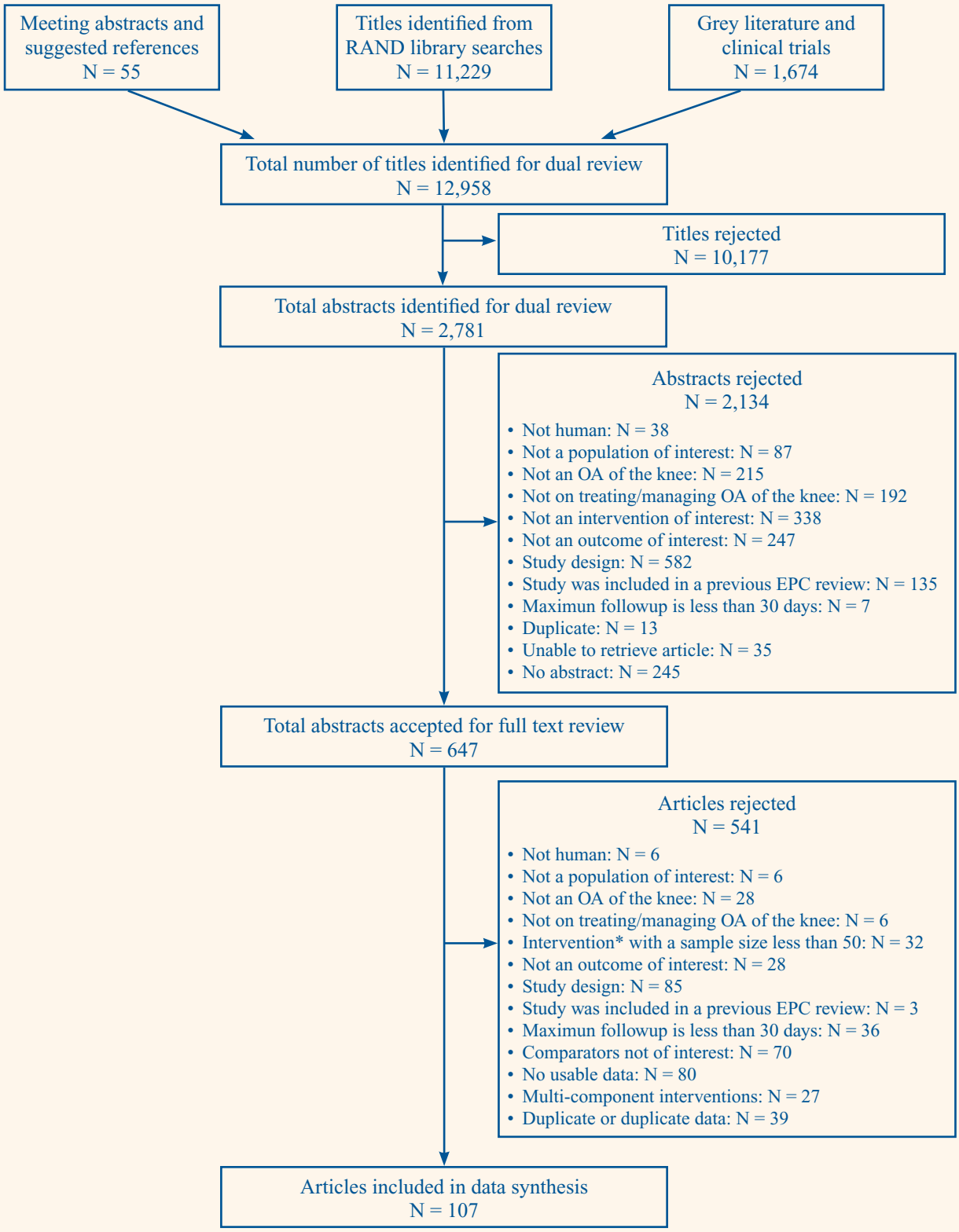

Figure notes: *Studies of glucosamine and/or chondroitin that enrolled fewer than 50 participants were excluded; EPC = Evidence-based Practice Center; OA = osteoarthritis

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)			

Table A. Summary strength of evidence (continued)

Intervention/Follow-up	Pain	Function	WOMAC Total	Quality of Life	Other
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					
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

Table A. Summary strength of evidence (continued)

Intervention/Follow-up	Pain	Function	WOMAC Total	Quality of Life	Other
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; 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 supporting benefits of tai chi for a composite measure of function but not pain, quality of life, or other measures of function.	Low-strength evidence supporting a beneficial effect of Tai chi on short- and medium-term pain and function

Table B. Findings in relation to what is already known (continued)

Intervention	Prior Findings	Findings of the Current Review
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.

Table B. Findings in relation to what is already known (continued)

Intervention	Prior Findings	Findings of the Current Review
PEMF	The 2012 review found beneficial effects on global assessment but no effects on pain, function, or other outcomes.	A small, nonstatistically significant benefit for short-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.

Full Report

This executive summary is part of the following document: 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.

AHRQ Pub. No.17-EHC011-1-EF
May 2017
www.ahrq.gov