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LITERATURE REVIEW

Effects of exercise on knee osteoarthritis: A systematic review

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Abstract

Background: Knee osteoarthritis is the most common joint disease and a major cause of functional limitation and pain in adults. The aim of this literature review is to review the existing evidence regarding the impact of exercise in people with knee osteoarthritis concerning physical and functional outcomes. The secondary aim is to provide both healthcare professionals and patients with updated and high-quality recommendations for the management of this condition.

Methods: A systematic search was performed at Pubmed, Scopus and Web of Science databases, limiting the studies to English, French and Portuguese language, from 2010 to May 2020. Eligible studies were randomized control trials or clinical control trials that compared an intervention consisting of an exercise programme in adult participants with knee osteoarthritis against no intervention.

Results: A total of 4499 studies were retrieved and 19 articles met the inclusion criteria. Beneficial effects of exercise were found on pain and strength. Regarding function, functional performance and quality of life, evidence is controversial. Both strengthening and aerobic exercise showed positive effects and both aquatic and land-based programmes presented improvement of pain, physical function and quality of life. Relatively to stretching, plyometric and proprioception training, no concrete conclusions can be taken.

Conclusion: Exercise programmes appear to be safe and effective in knee osteoarthritis patients, mainly regarding pain and strength improvement. Pilates, aerobic and strengthening exercise programmes performed for 8–12 weeks, 3–5 sessions per week; each session lasting 1 h appear to be effective. Both aquatic and land-based programmes show comparable and positive effects.

KEYWORDS
aerobic exercise, exercise, hydrotherapy, knee osteoarthritis, strength training

1 | INTRODUCTION

Knee osteoarthritis (OA) is the most common joint disease and a major cause of functional limitation and pain in older adults (Bricca, Juhl, Steultjens, Wirth, & Roos, 2019; de Rooij et al., 2016; McAlindon et al., 2014; O'Neill, McCabe, & McBeth, 2018; Tanaka, Ozawa, Kito, & Moriyama, 2014). The OA prevalence has doubled since the mid-20th century with an expected higher incidence in the future (Bricca et al., 2019).

Although the risk factors for the development of OA can be categorized as either systemic (including age, gender, obesity, genetics and ethnicity) or mechanical (including joint structure/

alignment, trauma, physical activity and occupation) (Huang, Guo, Xu, & Zhao, 2018; O'Neill et al., 2018; Palazzo, Nguyen, Lefevre-Colau, Rannou, & Poiraudeau, 2016), the cause of OA is still not clear (Huang et al., 2018).

Knee OA has long been considered a 'wear and tear' disease leading to loss of cartilage (de Rezende & de Campos, 2013); however, it has been shown cartilage undergoes a cycle of breakdown and repair. The imbalance between cartilage natural degradation and synthesis is thought to be the mechanism behind knee OA (Sandell & Aigner, 2001).

Furthermore, knee muscles, tendons, ligaments and joint capsules in patients with knee OA become weakened and damaged, with a decrease of proprioceptive sensation (Jeong et al., 2019; Van Ginckel, Hall, Dobson, & Calders, 2019). These physiological alterations lead to joint pain, stiffness, swelling, muscle weakness, reduction in quality of life (QoL) and physical disability such as difficulty with walking, climbing stairs, and sitting and rising from a chair (de Rooij et al., 2016; Fransen et al., 2015; Kolasinski et al., 2019; Kus & Yeldan, 2019; Lu et al., 2015; O'Neill et al., 2018; Zampogna et al., 2020).

Currently, no cure for OA is known (Fransen et al., 2015; Huang et al., 2018); however, symptomatology relief should be the focus of OA treatment (Tanaka et al., 2014). National Institute for Health and Care Excellence (NICE) recommends taking always an holistic approach into account when assessing and treating people with knee OA (NICE, 2020). Thus, exercise results in numerous systemic and local effects, some of which have been investigated among people with knee OA (Fransen et al., 2015).

Exercise is a core treatment for knee OA (NICE, 2020). Based on several systematic reviews and meta-analyses, all types of exercise could significantly relieve knee OA joint pain and improve physical function (Bartels et al., 2016; Bartholdy et al., 2017; Brosseau et al., 2017; Dong et al., 2018; Fransen et al., 2015; Hislop, Collins, Tucker, Deasy, & Semciw, 2020; Jeong et al., 2019; McAlindon et al., 2014). As it is still unclear which programme is more effective in treating knee OA, it is important to explore the effects of exercise programmes or other treatment options for patients with knee OA (Dong et al., 2018).

Systematic reviews of randomized controlled trials (RCTs) provide the highest quality of evidence for assessing effectiveness and harms of treatments (Bricca et al., 2019). Theoretical findings supported by current evidence may help the development of effective interventions in physiotherapy for knee OA.

Despite the existence of systematic reviews that address the effects of exercise programmes on knee OA patients, this topic is so complex and its prevalence so significant that a constant update of the scientific evidence is required.

Therefore, the aim of this systematic review is to contribute with an updated review of the existing evidence regarding the impact of all types of exercise in people with knee OA concerning physical and functional outcomes, when compared to no intervention. The secondary aim is to provide both healthcare professionals and knee OA patients with updated and high-quality recommendations for the management of this condition.

2 | METHODOLOGY

2.1 | Literature search

The literature search was conducted in two stages. For stage one, an initial electronic search was performed, and studies were evaluated for inclusion. Stage two consisted of a hand search of the reference lists of the articles selected in stage one. The electronic search was conducted on the month of May 2020, using predefined search terms and was restricted to English, French and Portuguese language publications found in the following databases: Pubmed, Web of Science and Scopus. Articles were limited to human studies published between January 2010 and May 2020. Combinations of the following keywords were used without language restriction: knee; osteoarthritis; exercise; aerobic; strength; stretching; hydrotherapy; rehabilitation. PubMed search was conducted using MeSH terms and Title/Abstract. In Web of Science was used TS (Topic) and in Scopus was used TITLE-ABS-KEY.

2.2 | Study selection

Once the search had been completed, titles and abstracts of the retrieved articles were reviewed by F and M. For the final inclusion, the articles had to fulfil all of the following criteria:

1. Been published in a peer-review journal as a full article or an abstract with sufficient detail to extract the main attributes of the study;
2. Been RCTs or clinical control trials (CCTs);
3. Had an intervention consisting of an exercise programme;
4. Had adult participants with knee OA, specifically in the tibiofemoral joint, with no previously scheduled or planned surgery;
5. Defined osteoarthritis as an orthopaedic degenerative process, not associated with any systemic problems;
6. No reported history of recent fracture to lower limbs;
7. Not undergoing any other formal or informal rehabilitation at the time of the study.

Studies were excluded if:

1. Data extraction was impossible;
2. Had no control group;
3. Had a control group different than usual care, education or no intervention at all.
4. Participants were submitted to surgical procedures, immobilization or any treatment of the lower limbs, such as knee intra-articular steroid injections;
5. Participants had any concurrent pathologies affecting the knee;
6. Participants had any neurological or cardiovascular conditions, except hypertension.

2.3 | Assessment of methodological quality

The two reviewers (F and M) assessed the methodological quality of each study against Cochrane scale.

The tool for assessing risk of bias is a domain-based evaluation, in which critical assessments are made separately for different domains as random sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting (Higgins et al., 2019). Each one of the domains was assessed as (i) low risk of bias if there were no methodological questions or if, existing, were unlikely to influence the outcome; (ii) unclear if no information was available and (iii) high risk if there was the possibility of a major influence on outcomes.

2.4 | Data extraction and synthesis

Titles and abstracts were screened by F and M to identify potentially eligible studies and full reports obtained. Full reports were assessed independently by F and M and a third reviewer (AC) against the eligibility criteria. Discrepancies in judgement were resolved by consensus with consulting of AC. If any item was unclear, F and M contacted the authors by email to clarify the issue. Those two reviewers independently extracted relevant data from the included studies.

The study characteristics extracted included information on the target population (gender, history of the condition, sample size, etc.); pathology (instruments, criteria, definitions); exercise programme; and outcome measures and significant findings.

Where feasible, the core findings of each article were expressed as effect sizes (ES). If possible, these measures were extracted directly from the article. For articles in which this information was not presented, as was generally the case, ES were calculated (95% confidence intervals) using mean values and a pooled standard deviation in accordance with the methods described by Cohen. ES between 0.2 and 0.49 can be interpreted as weak, 0.5–0.79 as medium, and greater than 0.8 as strong (Espirito Santo & Daniel, 2015).

3 | RESULTS

3.1 | Study selection

The initial search retrieved 4499 articles from electronic databases. After removing duplicates (n = 1277), 3222 articles were screened. From those articles, 3096 were excluded based on title and abstract. Therefore, 126 full articles were examined as potentially eligible. After excluding 107 full-text articles due to intervention (n = 48), population (n = 29), study design (n = 16), intervention and population (n = 10), outcome (n = 2), and language (n = 2), 19 articles met the eligibility criteria and were included in this systematic review for a qualitative synthesis. The percentage of agreement between both reviewers was 98% and any disagreement was resolved by discussion. When the consensus couldn't be reached, it was solved by AC. All 19 articles were RCTs. The selection of the studies is described on flow chart, annexed on Figure A1. The characterization of the studies can be found in Table 1.

3.2 | Assessment of methodological quality of studies

All studies were assessed according to Cochrane's guidelines for RCTs and CCTs (Higgins et al., 2019). Figure A2 reveals an overall assessment of the quality of the studies.

Concerning selection bias, most of the studies don't give information about the way the random sequence generation was performed, with only five being considered low risk of bias (DeVita et al., 2018; Dias et al., 2017; Karadağ, Taşci, Doğan, Demir, & Kiliç, 2019; Shellington, Gill, Shigematsu, & Petrella, 2019; Silva et al., 2015). However, most of the studies describe how the allocation concealment was done, being considered low risk of bias. Only six studies lack information about it, leaving the possibility of bias unclear (DeVita et al., 2018; Ha, Yoon, Yoo, Kang, & Ko, 2018; Huang et al., 2020; Karadağ et al., 2019; Liu et al., 2019; Mazloum, Rabiei, Rahnama, & Sabzehparvar, 2018).

Barely one study gives information about procedures for blinding of outcome patients (Lai, Zhang, Lee, & Wang, 2018) being considered as having a low risk for bias, while seven studies report that patients were not blinded to the procedures, being considered high risk for bias (Henriksen et al., 2014; Mazloum et al., 2018; Munukka et al., 2016; Shellington et al., 2019; Silva et al., 2015; Simão et al., 2012; Vincent, Vasilopoulos, Montero, & Vincent, 2019). The remaining studies fail to give information about it, leaving the possibility of bias unclear.

Similarly, only two studies give information about procedures for blinding of outcome providers (Lai et al., 2018; Munukka et al., 2016) whereas four studies were considered as having high risk of bias (Mazloum et al., 2018; Shellington et al., 2019; Silva et al., 2015; Simão et al., 2012). The other 13 studies were judged as unclear risk of bias.

On the other hand, the majority of studies report blinding of the outcome assessors, with only two studies being considered high risk of bias (Shellington et al., 2019; Vincent et al., 2019) and the remaining ones unclear risk of bias (Braghin, Libardi, Junqueira, NogueiraBarbosa, & de Abreu, 2018; DeVita et al., 2018; Ha et al., 2018; Huang et al., 2020; Karadağ et al., 2019; Liu et al., 2019).

All RCTs were judged as low risk for selective reporting (reporting bias) and drop-outs were defined properly in all studies, except in one study which left the possibility of bias unclear (Ha et al., 2018).

Regarding attrition bias relatively to intention-to-treat analysis, most of the studies were judged as showing unclear risk of bias, while five were considered low risk (de Oliveira, Peccin, da Silva, de Paiva

Teixeira, & Trevisani, 2012; Hunt et al., 2013; Imoto, Peccin, & Trevisani, 2012; Munukka et al., 2016; Vincent et al., 2019) and one high risk (Simão et al., 2012).

3.3 | Participants

Of all 19 articles included in this review, a total of 1126 participants with knee OA engaged in the studies, of which 572 were involved in an exercise programme and 460 were controls. Sample size per intervention group varied between a minimum of 9 (Ha et al., 2018; Hunt et al., 2013) and a maximum of 50 participants (de Oliveira et al., 2012; Imoto et al., 2012). Sample size per control group varied between a minimum of 8 (Ha et al., 2018; Hunt et al., 2013) and a maximum of 50 participants (de Oliveira et al., 2012; Imoto et al., 2012). Participants' age varied between 40 (Liu et al., 2019) and 82 years old (Simão et al., 2012).

3.4 | Criteria

All participants of the studies had to be diagnosed with knee OA. These diagnoses were made according the American College of Rheumatology (ACR) (de Oliveira et al., 2012; Dias et al., 2017; Hunt et al., 2013; Imoto et al., 2012; Karadağ et al., 2019; Silva et al., 2015; Vincent et al., 2019), the Kellgren–Lawrence Scale (Braghin et al., 2018; de Oliveira et al., 2012; Huang et al., 2020; Imoto et al., 2012; Liu et al., 2019; Munukka et al., 2016; Vincent et al., 2019), the American Rheumatism Association (Liu et al., 2019) or only based on radiology (DeVita et al., 2018; Henriksen et al., 2014; Mazloum et al., 2018; Simão et al., 2012; Wang et al., 2011). Two studies don't specify how diagnoses were made (Ha et al., 2018; Shellington et al., 2019).

From the retrieved studies, four (Braghin et al., 2018; Ha et al., 2018; Hunt et al., 2013; Karadağ et al., 2019) don't define age as an inclusion criteria. Considering the remaining studies, 40 years old was the minimum age required to participate (de Oliveira et al., 2012; DeVita et al., 2018; Dias et al., 2017; Henriksen et al., 2014; Huang et al., 2020; Imoto et al., 2012; Lai et al., 2018; Liu et al., 2019; Mazloum et al., 2018; Munukka et al., 2016; Shellington et al., 2019; Simão et al., 2012; Vincent et al., 2019; Wang et al., 2011), with one exception which allowed participants older than 18 to engage on it (Silva et al., 2015).

Additionally, some RCTs required that participants were not undergoing physiotherapy or any other rehabilitation treatment in the months previous to the study (Karadağ et al., 2019; Dias et al., 2017; Ha et al., 2018; Huang et al., 2020). Others only integrate people with crepitus and morning stiffness lasting 30 min or less (Simão et al., 2012) and/or people who had reported pain on the previous month (Mazloum et al., 2018; Hunt et al., 2013). Some studies used additional criteria such as having varus alignment (Hunt et al., 2013), not using any walking support (Dias et al., 2017), a score below 14 Beck Depression Inventory (BDI) II (Liu et al., 2019) and body mass index (BMI) between 19 and 35 kg/m^2 (DeVita et al., 2018; Henriksen et al., 2014).

3.5 | Outcome variables and measurement instruments

The 19 RCTs involved in our systematic review assessed a wide range of outcome variables: pain (n = 16), body function (n = 15), QoL (n = 6), pressure–pain thresholds (PPTs) and indices of temporal summation (TS) (n = 1), range of motion (ROM) (n = 1), functional performance (n = 10), strength (n = 7), proprioception (n = 2), VO_2 max (n = 2), leisure activities (n = 2), balance (n = 3), falls and fear of falling (n = 1), and other symptoms (n = 11). This review will focus primarily on pain, strength, function, functional performance and QoL outcomes.

For pain assessment, different instruments were used, such as Knee Injury and Osteoarthritis Outcome Score (KOOS) (Henriksen et al., 2014; Liu et al., 2019; Munukka et al., 2016; Wang et al., 2011), Visual Analogue Scale for Pain (VAS-P) (Karadağ et al., 2019), Western Ontario and McMaster Universities Arthritis Index (WOMAC) (Braghin et al., 2018; de Oliveira et al., 2012; DeVita et al., 2018; Dias et al., 2017; Ha et al., 2018; Karadağ et al., 2019; Shellington et al., 2019; Simão et al., 2012; Vincent et al., 2019), Lequesne Algofunctional Index (de Oliveira et al., 2012; Mazloum et al., 2018; Silva et al., 2015) and Numerical Rating Scale (Imoto et al., 2012). PPTs and TS were assessed using cuff pressure algometry (Henriksen et al., 2014).

Considering function, KOOS (Liu et al., 2019; Henriksen et al., 2014; Munukka et al., 2016; Wang et al., 2011), WOMAC (DeVita et al., 2018; Dias et al., 2017; Ha et al., 2018; Karadağ et al., 2019; Shellington et al., 2019) and Lequesne Algofunctional Index (Silva et al., 2015; Mazloum et al., 2018; de Oliveira et al., 2012) were the instruments chosen to evaluate.

A total of six studies assessed the QoL using KOOS (Henriksen et al., 2014; Liu et al., 2019; Munukka et al., 2016; Wang et al., 2011) and 36-item Short Form Health Survey (SF-36) (Silva et al., 2015; Imoto et al., 2012).

In order to evaluate functional performance, the tools applied were the 6-Minute Walk Test (6MWT) (Shellington et al., 2019; Silva et al., 2015; Simão et al., 2012; Wang et al., 2011), Step Test Exercise Prescription Test (STEP Test) (Shellington et al., 2019), Gait Speed Test (Simão et al., 2012), Timed Up-and-Go (TUG) (de Oliveira et al., 2012; Imoto et al., 2012; Shellington et al., 2019; Silva et al., 2015), Chair-stand (Shellington et al., 2019; Silva et al., 2015), Sit-and-Reach (Silva et al., 2015), walking for 15 m (Mazloum et al., 2018), standing up a chair and walking for 15 m (Mazloum et al., 2018), going up and down 11 stairs (Mazloum et al., 2018), Step Up/Over (Braghin et al., 2018), and motion analysis systems (DeVita et al., 2018; Hunt et al., 2013).

Concerning strength evaluation, isokinetic tests (DeVita et al., 2018; Dias et al., 2017; Ha et al., 2018; Huang et al., 2020; Hunt et al., 2013; Munukka et al., 2016) and one repetition maximum (RM) for

TABLE 1 Characteristics of included studies

Autor	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
Liu et al. (2019)	RCT	140 participants were randomized to Tai Chi group (*n* = 35); Baduanjin group (*n* = 35); stationary cycling group (*n* = 35); and control group (*n* = 35). Only 108 participants concluded the study (Tai Chi group (*n* = 28); Baduanjin group (*n* = 29); stationary cycling group (*n* = 27); and control group (*n* = 24)). Female = 83 and Male = 25.	Tai Chi group (*n* = 28) Age = 40–70 Baduanjin group (*n* = 29) Age = 40–68 Stationary cycling group (*n* = 27) Age = 40–70 Control group (*n* = 24) Age = 40–70	40–70 years old; diagnosis of chronic knee OA in the right or left knee based on the diagnostic criteria of the American Rheumatism Association by an orthopaedic physician; Grade 2 or 3 knee OA on the Kellgrene–Lawrence scale (radiologically confirmed); and BDI II score <14.	Stationary cycling

	Programme duration/ frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
	5 days a week for 12 weeks, each session lasting 1 h	KOOS Blood inflammation markers (Serum BDNF, IFN-g, PD-1, and TIM-3)	Compared to the control group, stationary cycling groups had significantly increased KOOS pain sub-score (pain reduction) and serum programmed death 1 (PD-1) concentrations; decreased right PAG rsFC with the medial orbital prefrontal cortex, and the decreased rsFC was associated with improvements in knee pain; decreased left VTA-left DLPFC rsFC; and grey matter volume in the medial orbital prefrontal cortex was significantly increased.	Cycling group versus control group ES between 0.2 and 1.2	Exercise can simultaneously modulate the rsFC of the descending opioidergic pathway and reward/motivation system and blood inflammation markers. Elucidating the shared and unique mechanisms of different exercise modalities may facilitate the development of exercise-based interventions for chronic pain.

	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
Henriksen et al. (2014)	RCT	60 participants initiated the study and were randomized to an exercise therapy (*n* = 31) and a control group (*n* = 29). 48 participants concluded the study (exercise therapy (*n* = 25); control group (*n* = 23)). Female = 39 and Male = 9.	Exercise therapy group (*n* = 25) Age (years) = 65.0 ± 8.9 Height (m) = 1.69 ± 0.08 Weight (kg) = 82.7 ± 13.8 BMI (kg/m^2) = 28.9 ± 4.1 Control group (*n* = 23) Age (years) = 62.3 ± 7.1	Adults aged 40 years or older, with a clinical diagnosis of tibiofemoral OA confirmed by radiography, assessed by an experienced radiologist, and a body mass index between 20 and 35 kg/m^2.	10-min warm-up phase (bicycle ergometer at moderate intensity) followed by a circuit training programme focusing on strength and coordination exercises of the trunk, hips and knees. The exercises were performed with free weights, elastic rubber bands, or body weight as resistance.

(Continues)

TABLE 1 (Continued)

	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
			Height (m) = 1.71 ± 0.09 Weight (kg) = 82.8 ± 15.8 BMI (kg/m^2) = 28.2 ± 4.6		

	Programme duration/frequency	Outcome measurement	Outcomes	Effect Sizes	Conclusion
	1-h sessions, three times weekly for 12 weeks	Cuff pressure algometry: PPTs and TS of pain KOOS	Compared to the control group, participants in the exercise group exhibited higher PPTs at follow-up and reduced their TS of pain upon sustained noxious pressure stimulation, despite being stimulated at a higher pressure at follow-up due to their increase in PPT and having higher TS at baseline. Mean group differences in the change from baseline were 3.1 kPa for the PPT, 2608 mm *x* seconds for TS, and 6.8 points for KOOS pain, all in favour of exercise therapy. In KOOS symptoms, albeit not reaching statistical significance, a group difference in the change from baseline was observed in favour of exercise therapy.	Exercise group versus control group PPTs ES = 0.62 favouring exercise therapy TS ES = 0.62 favouring exercise therapy KOOS pain ES = 0.71 favouring exercise therapy KOOS symptoms ES = 0.56 favouring exercise therapy	PPTs, TS and self-reported pain are reduced among patients completing a 12-week supervised exercise programme compared to a no attention control group. These results demonstrate beneficial effects of exercise on basic pain mechanisms and further exploration may provide a basis for optimized treatment.

	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
Karadağ et al. 2019	RCT	72 participants were randomized to a heat application group (*n* = 18), an exercise group (*n* = 17), an exercise after heat application group (*n* = 19) and a control group (*n* = 18). 62 participants concluded the study (heat application group (*n* = 15), exercise group (*n* = 15), exercise after heat application group (*n* = 15) and control group (*n* = 17)). Female = 52 and Male = 10.	Exercise group (*n* = 15) Age (years) = 58.73 ± 10.28 Exercise after heat application (*n* = 15) Age (years) = 57.13 ± 11.30 Control group (*n* = 17) Age (years) = 58.52 ± 10.95	According to ACR, criteria, patients who were diagnosed with bilateral knee OA for at least 6 months; did not have any communication and psychiatric problem; VAS-P scores of 4 and above according to the pain scale; did not have acute trauma, inflammation or oedema on their legs; did not have malignity, did not have circulatory disorder and peripheral vascular disease; did not receive intra-articular steroid treatment and physical therapies in the last 6 months.	Exercise group: Patients were shown seven movements specified by the consultant physiotherapist to strengthen their muscles (in standing, sitting, lying positions). They were delivered brochures and were asked to do those exercises at home. Exercise after heat application: Patients were told to do the recommended exercises after performing hot application on both knees with hot-packs for 20 min.

TABLE 1 (Continued)

Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
Twice a day (in the morning and evening), 5 days a week, for 4 weeks	VAS-P WOMAC OA	Both groups had decreases in VAS-P and Western Ontario and McMaster Universities osteoarthritis index pain, stiffness, and function scores when compared with the control group. This decrease in VAS-P and WOMAC OA scores was mostly in the exercise group, but this condition was not statistically significant.	Exercise group versus control group WOMAC pain ES = 0.9 WOMAC stiffness ES = 0.93 WOMAC disability ES = 0.91 VAS-P ES = 0.92 Heat + exercise versus control group WOMAC pain ES = 0.92 WOMAC stiffness ES = 0.81 WOMAC disability ES = 0.88 VAS-P ES = 0.94 Exercise group versus Heat+ exercise group WOMAC pain ES = 0.15 WOMAC stiffness ES = 0.71 WOMAC disability ES = 0.5 VAS-P ES = 0.1	Heat application and a home exercise programme reduced pain and enhanced function in patients with OA. As a result, it is recommended that nurses train patients with osteoarthritis on heat application and home exercises and encourage them to apply these practices.

(Continues)

TABLE 1 (Continued)

	Type of study	Sample (n)	Sample profile	Criteria	Exercise programme
Wang et al. (2011)	RCT	78 participants were randomized to an aquatic exercise group (n = 26); land-based exercise group (n = 26); and a control group (n = 26). Female = 67 and Male = 11.	Total (n = 78) Age (years) = 67.7 ± 5.9 Aquatic exercise group (n = 26) Age (years) = 66.7 ± 5.6 BMI (kg/m^2) = 26.6 ± 2.5 Land-based exercise group (n = 26) Age (years) = 68.3 ± 6.4 BMI (kg/m^2) = 25.4 ± 2.4 Control group (n = 26) Age (years) = 67.9 ± 5.9 BMI (kg/m^2) = 26.6 ± 2.08	Age over 55 years; diagnosed with knee OA by physician assessment based on symptoms and x-ray; consented to participate.	The land-based exercise group performed 60-min flexibility and aerobic training class, focused on joint in the trunk, shoulders, arms and legs and emphasizing the muscle groups of the upper and lower limbs as well as balance and coordination. The aquatic exercise group performed the same programme in water.

	Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
	3 times a week for 12 weeks	KOOS Goniometry 6MWT	Results showed statistically significant group-by-time interactions in pain, symptoms, sport/recreation and knee-related quality-of-life dimensions of KOOS, knee range of motions and the 6MWT. However, the aquatic group did not show any significant difference from the land group at both weeks 12 and 6 in pain reduction. Compared to the control group, the aquatic and the land group had significantly less problem with pain.	Aquatic group: KOOS pain ES = 0.11 KOOS symptoms ES = 0.21 KOOS ADL ES = 0.2 KOOS sport/recreation ES = 0.30 KOOS QQL ES = 0.23 OM knee extension ES = 0.25 ROM knee flexion	Both aquatic and land-based exercise programmes are effective in reducing pain, improving knee ROM, 6MWT and knee-related QoL in people with knee osteoarthritis. The aquatic exercise is not superior to land-based exercise in pain reduction.

TABLE 1 (Continued)

Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
			ES = 0.26	
			6MWT	
			ES = 0.33	
			Land group:	
			KOOS pain	
			ES = 0.23	
			KOOS symptoms	
			ES = 0.37	
			KOOS ADL	
			ES = 0.37	
			KOOS sport/recreation	
			ES = 0.28	
			KOOS QQL	
			ES = 0.23	
			ROM knee extension	
			ES = 0.45	
			ROM knee flexion	
			ES = 0.22	
			6MWT	
			ES = 0.32	
			Aquatic versus land group	
			KOOS pain	
			ES = 0.2	
			KOOS symptoms	
			ES = 0.06	
			KOOS ADL	
			ES = 0.2	
			KOOS sport/recreation	
			ES = 0.05	
			KOOS QQL	

(Continues)

TABLE 1 (Continued)

	Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
				ES = 0.04 ROM knee extension ES = 0.12 ROM knee flexion ES = 0 6MWT ES = 0.03	

	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
Vincent et al. (2019)	RCT	90 participants were randomized to a CNC RT (*n* = 28), an ECC RT (*n* = 30) and a control group (*n* = 32). 53 participants concluded the study (CNC RT (*n* = 17), ECC RT (*n* = 19) and control (*n* = 17)).	CNC RT (*n* = 28) Age, years = 69.5 ± 6.5 BMI (kg/m^2) = 32.8 ± 7.4 ECC RT (*n* = 30) Age, years = 66.8 ± 5.4 BMI (kg/m^2) = 28.7 ± 6.6 Control (*n* = 32) Age, years = 68.6 ± 7.2 BMI (kg/m^2) = 30.1 ± 6.2	Men and women age 60–85 years; presence of knee OA (using American College of Rheumatology criteria) for ≥6 months; knee pain primarily due to tibiofemoral OA and not from patellofemoral OA; bilateral standing anterior–posterior radiograph demonstrating Kellgren and Lawrence OA grade 2 or 3 out of the target knee; willing and able to participate in regular exercise for 4 months; free from musculoskeletal limitations that would preclude resistance exercise participation (i.e., joint contractures, fractures), and free of abnormal cardiovascular responses during the screening-graded maximal walk test.	CNC RT Two resistance exercise sessions per week, and one set of each exercise was completed in each session: leg press, knee flexion, knee extension, chest press, seated row, overhead press, biceps curl, and calf press. Each set contained 12 repetitions performed at a resistance load of 60% of the concentric 1RM for that exercise. ECC RT The same programme but each set consisted of eight repetitions.

	Programme duration/frequency	Outcome measurement	Outcomes	Effect Sizes	Conclusion
	Two times per week, for 4 months	WOMAC 1 RM	Both CNC RT and ECC RT groups showed 16%–28% improvement relative to the waitlist, no-exercise control group for all leg strength measures. The rate of weekly strength gain was greater for CNC RT than for ECC RT for leg press and knee flexion but not knee extension. There were no significant differences in WOMAC total and subscores across groups over time. Leg press strength change was the	Not possible to calculate due to lack of data.	Both resistance training types effectively increased leg strength. Knee flexion and knee extension muscle strength can modify function and pain symptoms irrespective of muscle contraction type. Which mode to pick could be determined by preference, goals, tolerance to the contraction type, and equipment availability.

TABLE 1 (Continued)

	Programme duration/frequency	Outcome measurement	Outcomes	Effect Sizes	Conclusion
			greatest contributor to change in WOMAC total scores. The change in knee flexion strength from baseline to month 4 was a significant predictor of the change in WOMAC pain subscore. Both modes of strength training were well tolerated.		

	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
Lai et al. (2018)	RCT	40 participants initiated the study but only 34 participants concluded it (strength exercise group (*n* = 18) and a control group (*n* = 16)). Female = 32 and Male = 2.	Strength exercise group (*n* = 18): Age (years) = 64.07 ± 4.45 Height (cm) = 157.89 ± 5.96 Weight (kg) = 56.17 ± 9.6 BMI (kg/m^2) = 22.47 ± 3.16 Control group (*n* = 16) Age (years) = 63.20 ± 3.69 Height (cm) = 157.18 ± 6.04 Weight (kg) = 58.47 ± 6.39 BMI (kg/m^2) = 24.27 ± 1.96	Mild-to-moderate knee OA (Lequesne knee score = 1–7); ages ranged from 50 to 70 years.	Each session constituted a warm-up, squat training with the knees bent at 30° and 60° and a cool-down.

	Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
	Three sessions a week, for 8 weeks	Knee and ankle proprioception	Passive motion sense in knee flexion of participants in strength exercise group significantly improved with significant difference between groups. No significant differences of passive motion senses were found in knee extension and ankle between strength exercise and control groups.	Plantarflexion of ankle ES = 0.003 Dorsiflexion of ankle ES = 0.002 Varus of ankle ES = 0.017 Valgus of ankle ES = 0.004 Flexion of knee ES = 0.124 Extension of knee ES = 0.004	Eight weeks of squat training improved the motion sense of knee flexion in patients with knee OA. Therefore, squat training might be an effective proprioception training method for individuals with knee OA.

(Continues)

TABLE 1 (Continued)

	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
Ha et al. (2018)	RCT	17 participants randomized to an exercise group ($n = 9$) and a control group ($n = 8$).	Exercise group ($n = 9$): Age (years) = 60.89 ± 5.06 Height (cm) = 156.89 ± 6.99 Weight (kg) = 61.79 ± 9.94 BMI (kg/m^2) = 25.18 ± 4.31 Control group ($n = 8$) Age (years) = 61.25 ± 1.91 Height (cm) = 154.14 ± 5.04 Weight (kg) = 58.20 ± 10.95 BMI (kg/m^2) = 24.63 ± 5.33	People diagnosed with knee OA; people who received a doctor's consent to participate in the exercise programme; people who did not participate in regular exercise or other exercise programmes for the past 6 months.	Aquatic exercise programme in an indoor pool followed by a preparation exercise, a main exercise, and a healing exercise. The preparation and the grooming exercise were performed for 10 min each for jumping, walking and stretching.

Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
Three times a week for 60 min a day, for 12 weeks.	Anthropometric and metabolic syndrome risk factors (weight; BMI; body fat percentage; waist circumference; systolic and diastolic blood pressure; fasting blood glucose; glycosylated haemoglobin; triglycerides; high-density lipoprotein cholesterol; C-reactive protein)Knee isokinetic function test (right knee-extensor peak torque/body weight; left knee-extensor peak torque/body weight; right knee-flexion peak torque/body weight; left knee-flexion peak torque/body weight) Cardiorespiratory test (VO_2 max)	There was no significant difference in the BMI, body fat percentage, waist circumference, systolic blood pressure, diastolic blood pressure, HDL-C, and CRP between the two groups. Fasting blood glucose, glycosylated haemoglobin, and triglyceride were significantly decreased in the risk factors of metabolic syndrome. The maximum oxygen uptake in cardiorespiratory fitness was not significantly different. The left and right extensor muscles of knee isokinetic function increased significantly. There was no significant difference in flexor muscles. Osteoarthritis index was significantly improved in stiffness and physical function.	Weight ES = 0.12 BMI ES = 0.007 Body fat ES = 0.012 WC ES = 0.13 SBP ES = 0.16 DBP ES = 0 FBG ES = 0.27 HbA ES = 0.27 TG ES = 0.06 HDL-C	Aquatic exercise can be regarded as an effective exercise programme for the management of metabolic syndrome, improvement of muscle function, and improvement of osteoarthritis index in osteoarthritis women.

TABLE 1 (Continued)

Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
			ES = 0.05	
			CRP	
			ES = 0	
			VO2 max (ml/kg/min)	
			ES = 0.34	
			Rt knee EX TQ/BW (Nm)	
			ES = 0.32	
			Lt knee EX TQ/BW (Nm)	
			ES = 0.27	
			Rt knee FX TQ/BW (Nm)	
			ES = 0.12	
			Lt knee FX TQ/BW (Nm)	
			ES = 0.12	
			WOMAC pain	
			ES = 0.27	
			WOMAC stiffness	
			ES = 0.37	
			WOMAC physical function	
			ES = 0.18	
			WOMAC total	
			ES = 0.23	
	Type of study	**Sample (*n*)**	**Sample profile**	**Criteria**	**Exercise programme**
Huang et al. (2020)	RCT	32 participants initiated the study and were randomized to a control group (n = 15) and a training group (n = 17). 26 concluded the study (training group (n = 16) and a control group (n = 10)).	Training group (n = 16) Age (years) = 67.94 ± 3.89 Height (cm) = 152.93 ± 4.68 Weight (kg) = 59.97 ± 6.86 Body mass index (kg/m^2) = 25.68 ± 3.17 Control group (n = 10)	Knee OA diagnosed by a physician; 45 years old or older; physically capable of entering exercise but have not previously taken part in any type of resistance training; able to participate safely in a moderately vigorous programme of physical activity.	Each session comprised of warm-up exercise (10 min), resistance training (40 min), and cool-down exercise (10 min). The resistance training was performed in a circuit manner with seven individual hydraulic

(Continues)

TABLE 1 (Continued)

Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
		Age (years) = 56.50 ± 9.64 Height (cm) = 155.50 ± 3.68 Weight (kg) = 61.41 ± 10.87 Body mass index (kg/m^2) = 25.48 ± 4.37		resistance machines interspersed with 60 s stepping aerobic exercise arranged alternatively. The seven hydraulic resistance machines included chest press/row, biceps curl/triceps extension, upright row/press, ab/back, hip abduction/adduction, leg press/curl, and leg extension/curl. Each participant was required to perform an eight-repetition, two-set with 1 min rest interval full ROM exercise.

Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
1-h session, 3 days per week, for 12 weeks	Maximum voluntary contraction (MVC) testing (via an isokinetic dynamometer) Contractile rate of force development (RFD) testingContractile impulse testing	The dynamic combined training programme was effective in improving the muscle strength. MVC and contractile RFD improved but did not reach statistical significance.	MVC ES = 1.5 RFD (0-30 ms) ES = 0.5 RFD (0-50 ms) ES = 0.5 RFD (0-100 ms) ES = 0.4 RFD (0-200 ms) ES = 0.8 Impulse (0-30 ms) ES = 0.3 Impulse (0-50 ms) ES = 0.3 Impulse (0-100 ms)	The dynamic combined training programme is effective for health promotion in older adults with knee OA.

TABLE 1 (Continued)

	Programme duration/ frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
				ES = 3.3 Impulse (0-200 ms) ES = 0.6	

	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
Da Silva et al. (2015)	RCT	41 participants were randomized to an intervention group (*n* = 19) and control group (*n* = 22). 30 participants concluded the study (intervention group (*n* = 15) and control group (*n* = 15). Female = 26 and Male = 4.	Intervention group (*n* = 15) Age (years) = 57 ± 6.01 Height (m) = 1.57 ± 0.09 Weight (kg) = 72.22 ± 11.43 BMI (kg/m^2) = 29.37 ± 4.10 Control group (*n* = 15) Age (years) = 60 ± 7.76 Height (m) = 1.54 ± 0.10 Weight (kg) = 69.43 ± 10.57 BMI (kg/m2) = 29.29 ± 5.00	Patients aged above 18 years with symptomatic clinical diagnosis of chronic knee OA (based on the criteria of the ACR) and moderate to very severe knee pain according to the Lequesne algofunctional index (scores ranging from 5 to 13).	Several physical activities (45 min): Warm-up for 10 min with a stationary bike and stretching; exercises for the strength of the lower and upper limbs; body mobility, functional, and balance exercises; and relaxation.

Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
1-h sessions, twice a week, for 8 weeks	Lequesne algofunctional indexPerformance tests (chair-stand, sit-and-reach, TUG, and 6MWT)36-Item short form health Survey (SF-36)	Analysis of covariance revealed significant post-intervention improvements of intervention group participants compared with control group participants on Lequesne total score and pain and function subdomains; SF-36 physical function, role physical, bodily pain, general health, vitality, and role emotional subdomains; and performance assessed by chair-stand, TUG, and 6MWT. Focusing on the primary outcome (Lequesne total score), after 8 weeks the mean ± standard deviation was 5.50 ± 2.98 for the intervention group and 7.87 ± 3.48 for the control group.	Lequesne total score ES = 0.34 Lequesne pain ES = 0.41 Lequesne distance ES = 0.41 Lequesne function ES = 0.1 SF-36 physical function ES = 0.38 SF-36 role physical ES = 0.64 SF-36 bodily pain	The presented rehabilitation programme reduced pain and improved QoL and function in patients with knee OA.

(Continues)

TABLE 1 (Continued)

	Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
				ES = 0.39	
				SF-36 general health	
				ES = 0.35	
				SF-36 vitality	
				ES = 0.4	
				SF-36 social function	
				ES = 0.03	
				SF-36 role emotional	
				ES = 0.5	
				SF-36 mental health	
				ES = 0.33	
				Chair-stand test	
				ES = 0.43	
				Sit-and-Reach test	
				ES = 0.28	
				TUG	
				ES = 0.6	
				6MWT	
				ES = 0.38	
	Type of study	**Sample (*n*)**	**Sample profile**	**Criteria**	**Exercise programme**
Munukka et al. (2016)	RCT	87 participants were randomized to an aquatic training group (n = 43) and a control group (n = 44). 84 participants concluded the study (aquatic training group (n = 42) and control group (n = 42)).	Aquatic training group (n = 43) Age (years) = 64 ± 2 Height (cm) = 162 ± 5 Weight (kg) = 69.6 ± 10.3 BMI (kg/m2) = 26.6 ± 3.8 Control group (n = 44) Age (years) = 64 ± 2 Height (cm) = 162 ± 5 Weight (kg) = 71.0 ± 11.3 BMI (kg/m2) = 27.1 ± 3.5	Post-menopausal woman aged 60–68 years; experiencing knee pain on most day; participates in intensive exercise twice a week; radiographic changes in tibiofemoral joint K/L I or II; no previous cancer or chemotherapy; no medical contraindications or other limitations to full participation in an intensive aquatic training program and complete transverse relaxation time (T2) data.	Supervised lower limb aquatic resistance training. Resistance of exercises was progressed with three different levels: Barefoot, small fins and large resistance boots, and the training leg performed all the movements without contact with the pool walls or bottom, i.e., non-weight bearing.

TABLE 1 (Continued)

Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
1-h session, three times a week for 16 weeks, for a total of 48 training sessions.	T2 relaxation time mappingDelayed gadolinium-enhanced magnetic resonance imaging of cartilageCardiorespiratory fitness (VO_2 peak, ml/kg/min)Isometric knee extension and flexion force (N) of the affected knee was measured using an adjustable dynamometer chairKOOSAccelerometer (daily physical activity)	After 4-month aquatic training, there was a significant decrease in both T2 1.2 ms and dGEMRIC index 23 ms in the training group compared to controls in the full thickness posterior region of interest of the medial femoral cartilage. Cardiorespiratory fitness significantly improved in the intervention group by 9.8%. There were no between group differences in the knee extension or flexion muscle force or in any domains of KOOS. There was no significant difference between the groups in physical activity as measured with accelerometers, excluding the intervention.	T2, ms Femur - Lateral Condyle - Central ES = 0.05 T2, ms Femur - Lateral Condyle - posterior ES = 0.74 T2, ms Femur - medial Condyle - Central ES = 0.18 T2, ms Femur - medial Condyle - posterior ES = 0.48 T2, ms Tibia – Lateral plateau - Central ES = 0.15 T2, ms Tibia – Medial plateau - Central ES = 0 dGEMRIC, ms Femur – lateral condyle – Central ES = 0.07 dGEMRIC, ms Femur – lateral condyle – Posterior ES = 0.08 dGEMRIC, ms Femur – medial condyle – Central ES = 0.34 dGEMRIC, ms Femur – medial condyle – Posterior ES = 0.53 dGEMRIC, ms Tibia– lateral plateau – Central ES = 0.03 dGEMRIC, ms Tibia– medial plateau – Central ES = 0.32	In post-menopausal women with mild knee OA, the integrity of the collagen-interstitial water environment (T2) of the tibiofemoral cartilage may be responsive to low shear and compressive forces during aquatic resistance training. Further, aquatic resistance training improves cardiorespiratory fitness.

(Continues)

TABLE 1 (Continued)

Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
			Estimated VO2 peak ES = 0.58 Force (N) extension ES = 0.27 Force (N) flexion ES = 0.07 KOOS pain ES = 0.30 KOOS other symptoms ES = 0.37 KOOS ADL ES = 0.39 KOOS sport ES = 0.27 KOOS QoL ES = 0.26	

	Type of study	Sample (n)	Sample profile	Criteria	Exercise program
Simão et al. (2012)	RCT	35 participants were randomized to a squat exercise on a vibratory platform (*N* = 12); Squat exercise (*N* = 11); Control group (*N* = 12). 31 participants completed the study (squat exercises on a vibratory platform (*N* = 10); Squat exercise (*N* = 10); Control group (*N* = 11)). Male = 4 and Female = 27.	Platform group (*n* = 10) Age = 75 ± 7.4 years Weight = 74.2 ± 10.7 kg Height = 1,56 ± 0,05 m BMI = 27.4 ± 9.7 kg/m^2 Squat group (*n* = 10) Age = 69 ± 3.7 years Weight = 73.4 ± 9.7 kg Height = 1,57 ± 0,08 m BMI = 29.8 ± 2.53 kg/m^2	Knee pain for most of the days in the previous month; osteophytes at the joint margins on radiographs; synovial fluid typical of OA (laboratory); age 40 years or older; crepitus on active joint motion; and morning stiffness lasting 30 min or less.	Squat exercise (maintaining the semi-full position (3 s) and the flexed position (3 s of isometric contraction) of the knees in each squat repetition) or Squat exercise on a vibratory platform (the frequency was varied from 35 to 40 Hz, the amplitude was 4 mm, and the acceleration ranged from 2.78 to 3.26 g). The volume of the training was increased during the 12 weeksBefore strength exercise, the subjects warmed up on exercise bikes for 10 min. At 70% HRmax.

TABLE 1 (Continued)

Type of study	Sample (n)	Sample profile	Criteria	Exercise program
		Control group (n = 11) Age = 71 ± 5.3 years Weight = 65.1 ± 10.5 kg Height = 1.56 ± 0.07 m BMI = 26.7 ± 2.74 kg/m^2		

Programme duration/frequency	Outcome measurement	Outcomes	Effect Sizes	Conclusion
12 weeks—3x/week, on alternate days.	Plasma soluble tumour necrosis factor-α receptors 1 (sTNFR1) and 2 (sTNFR2)WOMAC; Functional performance tests (6MWT; Berg balance scale; gait speed test).	The plasma concentrations of sTNFR1 and sTNFR2 showed a significant reduction in the platform group compared with the control group;The gait speed in the platform group was faster than in the squat group after training;No significant differences between the squat and the control group.	Control versus squat sTNFR1: 0.49 sTNFR2: 0.72 WOMAC: Pain: 0.27 Stiffness: 0.58 Function: 0.2 Berg balance scale: 0.23 6MWT: 0.6 Gait speed test: 0.2 Control VS platform sTNFR1: 0.53 sTNFR2: 0.44 WOMAC: Pain: 0 Stiffness: 0. Function: 0.27 Berg balance scale: 0 6MWT: 0.15 Gait speed test: 0.08 Squat VS platform sTNFR1: 0.11 sTNFR2: 0.21 WOMAC: Pain: 0.12	The addition of vibration training to squat exercise training improves static and dynamic balance and gait performance. Also, the addition of vibration training reduces the self-perception of pain and inflammatory markers in elderly patients with knee OA.

(Continues)

TABLE 1 (Continued)

Programme duration/frequency	Outcome measurement	Outcomes	Effect Sizes	Conclusion
			Stiffness: 0.45 Function: 0.39 Berg balance scale: 0.07 6MWT: 0.42 Gait speed test: 0.02	

	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
Dias et al. (2017)	RCT	73 participants were randomized to a hydrotherapy (*n* = 37) or a control group (*n* = 36). 65 participants concluded the study (hydrotherapy (*n* = 33) or a control group (*n* = 32).	Hydrotherapy group (*n* = 33) Age = 70.8 ± 5 years BMI = 30.5 ± 4.30 kg/m^2 Control group (*n* = 32) Age = 71 ± 5.20 years BMI = 30.0 ± 5.20 kg/m^2	Aged 65 years or older; diagnosed with OA in at least one knee based on the clinical and radiographic criteria of the ACR; no lower limb joint replacement surgery; no history of recent trauma in lower limbs; not to be using any walking support; not have received physiotherapy or any other rehabilitation treatment in the past 3 months; no cognitive limitations to do aquatic activities assessed by the Mini-Mental State test; no open wounds or skin disease and urinary or faecal incontinence.	Hydrotherapy (three stages: Warm-up (5 min), strengthening exercises (30 min), and a cool-down session (5 min). The participants performed lower limb strengthening exercises that included closed kinetic chain exercises using float as well as multidirectional walking tasks. Relaxation exercises were performed before living the pool); The volume of the training was increased: 1–3 sessions (2 sets, 20 reps); 4–6 sessions (3 sets, 20 reps); 7–9 sessions (4 sets, 20 reps) and 10–12 sessions (4 sets, 25 reps).

Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
6 weeks - 2x/week	WOMAC knee Extensor and knee flexor muscle performance (strength, power, and endurance) in the isokinetic test	Participants from the treatment group had significantly less knee pain and higher levels of function when compared to the control group. Participants from the treatment group had significantly more muscle strength of the knee flexors and extensors, respectively), more muscle power for the knee flexors, and more for resistance for the knee extensors. There were no other statistically significant between-group for muscle	WOMAC Pain: ES = 0.27 Function: ES = 0.32 Muscle strength Flexors: ES = 0.14 Extensors: ES = 0.08 Muscle power	Older women with knee OA are likely to have benefits from a course of hydrotherapy exercises.

TABLE 1 (Continued)

	Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
			power for the knee extensors and for resistance for the knee flexors.	Knee flexors: ES = 0.01 Knee extensor: ES = 0.09 Muscle resistance Knee extensors: ES = 0.17 Knee flexors: ES = 0.04	

	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise program
de Oliveira et al. (2012)	RCT	100 patients were randomized into two groups: Exercise group (*N* = 50) and instruction group (*N* = 50). 81 completed the study (exercise group (*N* = 43) or instruction group (*N* = 38)).	Exercise group (*n* = 50) Age = 61.50 ± 6.94 years BMI = 29.72 ± 4.11 kg/m^2 Instruction group (*n* = 50) Age = 58.78 ± 9.60 BMI = 30 ± 5.05 kg/m^2	Age between 50 and 75 years; OA classified as grade II and over based on the Kellgren & Lawrence radiological classification; knee OA diagnosed according to the ACR criteria.	The intervention included: Warm up for 10 min with a stationary bike; stretching of the hamstring muscle with the aid of an elastic band (3 sets of 30 s); and 3 sets of 15 repetitions of knee extension exercises, with 30–45-s intervals between the sets.

	Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
	8–2x/week	TUGWOMACLequesne index	In exercise group, statistically significant differences were observed in the TUG test scores; Comparing the groups, a statistically greater TUG test improvement was observed in exercise group as compared to instruction group; The exercise group showed a statistically significant improvement as compared to the instruction group in the WOMAC scores of pain, functionality, and stiffness, and in the Lequesne index.	TUG = 0.32Lequesne Index = 0.21WOMACPain: ES = 0.09Stiffness: ES = 0.27Function: ES = 0.18	Quadriceps strengthening exercises for eight weeks are effective to improve pain, function, and stiffness in patients with knee OA. Strengthening exercises combined with stretching and stationary bike should be implemented in rehabilitation programmes of patients with knee OA.

	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
Shellington et al. (2019)	RCT	22 participants with knee OA were divided into two groups: Square-Stepping exercise group (*N* = 10) or control group (*N* = 12). 19 participants concluded the study (Square-Stepping exercise group (*N* = 7) or control group (*N* = 12)). Male = 7 and	Square-Stepping exercise group (*n* = 10) Age = 69.7 ± 9.3 years BMI = 32.0 ± 7.2 kg/m2 Height = 163.8 ± 7.9 cm Weight = 88.9 ± 16.6 Kg	Participants were ambulatory; 45–85 years old; diagnosed with knee OA; WOMAC average pain score of 4 or greater for their index knee across five pain questions (each on a 0–10 pain scale); available twice weekly for the duration of the study.	Square-stepping exercise is a low-intensity training programme and can be considered a proprioception or neuromuscular training task. The participants are required to repeat it four times. The square-stepping exercise programme begins with beginner patterns and progresses to

(Continues)

TABLE 1 (Continued)

	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
		Female = 15.	Control group (*n* = 12) Age = 69.3 ± 5.9 years BMI = 29.6 ± 3.7 kg/m2 Height = 163.3 ± 9.6 cm Weight = 79.1 ± 13.2 Kg		intermediate and advanced patterns. The number of steps in a pattern ranges from 2 to 16 steps, and steps can be in any direction. During the 1-h sessions, a 5–10-min warm-up, and 5–10-min cool-down were done at the beginning and end to reduce the risk of injury, with a focus on stretching the muscles of the neck.

	Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
	24 weeks - 2x/week	WOMAC;Mobility (30-s chair stand and TUG);Balance (ABC and FAB scales);Leisure activities (cognitive and physical activities);Fitness (STEP [Step test exercise prescription] test); Walking speed (6MWT)	Comparing the groups, no significant differences or effects were observed in WOMAC (between groups at V1 and V2, controlling for V0). The SSE group trended towards improvements in the 30-s chair stand test at V1 and V2, controlling for V0, besides having no significant differences. The SSE group trended towards improvements in walking speed at V1 and V2, controlling for V0, besides having no significant differences. There was a close to positive effect on the ABC scale at V1, besides having no significant differences. There were no other statistically significant between-group differences for any other measurements on balance, mobility, leisure activities, or fitness.	Not possible to calculate due to lack of data.	The low attendance and recruitment demonstrated limited feasibility of SSE in adults with knee OA. Trends suggest the potential for SSE to improve lower extremity functional fitness and walking speed. This preliminary data may indicate that SSE can reduce functional limitations and falls risk in adults with knee OA as well as improve neuromuscular function and proprioception.

	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
DeVita et al. (2018)	RCT	31 patients were randomly allocated to quadriceps strengthening programme (*N* = 16) or no attention control group (*N* = 15). 30 participants concluded the study (strengthening programme (*N* = 15) or	Quadriceps strengthening programme (*n* = 15) Age = 58.1 ± 6.5 years BMI = 26.4 ± 4.0 kg/m2 Height = 1.73 ± 0.07 m Weight = 79.4 ± 14.8 Kg Control group (*n* = 15)	Clinical symptoms and radiographic findings of tibiofemoral OA were verified in one or both knees; participants were in general good health aged between 45 and 70 years; body mass index between 19 and 34 kg/m^2.	Quadriceps strengthening including leg extension, leg press and forward lunge exercise (3 sets of 10 reps with loads). The initial two weeks were performed at 60% 3RM, the following two weeks at 70% 3RM and the remaining 8 weeks at 85% 3RM.Participants performed 10min of warming up on a treadmill or stationary bicycle.

TABLE 1 (Continued)

Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
	no attention control group (*N* = 15)). Male = 12 and Female = 18.	Age = 56.2 ± 8.9 years BMI = 27.9 ± 3.9 kg/m2 Height = 1.73 ± 0.11 m Weight = 83.8 ± 18.7 Kg		

Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
1-h session, three times a week, for 12 weeks	Isokinetic muscle strength WOMAC (Pain and function)Gait variables: Peak quadriceps forceQuadriceps power and workMaximum quadriceps muscle forceKnee compression forces during walkingMaximum knee flexion and maximum internal knee extensor torqueWalking velocity	Quadriceps strength training produced significant group differences in quadriceps strength and pain, function and total WOMAC scores. Non-significant differences in the group difference scores for maximum quadriceps force and maximum compressive knee force during walking; Statistically significant effect in the difference score was evident for maximum negative quadriceps power in early stance, with a 36% increase in the training group compared to 1% decrease in the control group; The group differences in negative quadriceps work and maximum positive quadriceps power and work in early stance were not statistically significant; Maximum knee flexion and knee internal extension torque during loading phase were not statistically significantly different between groups; Walking velocity during the gait tests was statistically significantly increased by 3% in the training group compared to a 3% decrease the control group; Changes in maximum knee compression and maximum quadriceps force were inversely related to changes in pain and function.	ES for quadriceps muscle strength was 0.90;ES for WOMAC was over 1.00 for each variable;ES for maximum negative quadriceps power was 0.91;ES for walking velocity was 0.98;	Quadriceps strength training leads to increased muscle strength and improved symptomatic and functional outcomes but does not change quadriceps or knee joint biomechanics during walking. The biomechanical mechanism of improved health with strength training in knee OA patients remains unknown.

(Continues)

TABLE 1 (Continued)

	Type of study	Sample (n)	Sample profile	Criteria	Exercise program
Imoto et al. (2012)	RCT	100 patients were randomized into two groups: Exercise group (*N* = 50) or orientation group (*N* = 50). 81 patients concluded the study (exercise group (*N* = 43) or orientation group (*N* = 38). Male = 16 and Female = 65.	Exercise group (*n* = 43) Age = 61.50 ± 6.94 years BMI = 29.72 ± 4.11 kg/m2 Orientation group (*n* = 38) Age = 58.78 ± 9.60 years BMI = 30.00 ± 5.05 kg/m2	Age between 50 and 75 years; diagnosis of knee OA according to the criteria of the ACR based on history, physical examination and radiographic findings; knee x-ray in the last 12 months and grade 2 or above in the Kellgren and Lawrence radiographic classification.	The exercise sessions consisted of 10 min of warm-up on a stationary bicycle, ischiotibial stretching exercises and three series of 15 repetitions of knee extension exercises. The interval between series was from 30 to 45-s 50%–60% of the load was established for use in the strengthening exercises. However, the load was increased according to tolerance.

	Programme duration/frequency	Outcome measurement	Outcomes	Effect Sizes	Conclusion
	8 weeks- 2x/week30 to 40 min.	TUGNRSShort-form 36	Exercise group presented statistically significant reduction of pain intensity (NRS) and in the timing of the TUG test. There was statistically significant difference in exercise group when compared to orientation group in the NRS and TUG outcome.In exercise group, the evaluation of the items of the SF-36 QoL questionnaire showed statistically significant improvement in the aspects: Functional capacity, pain, physical aspects, general state of health and vitality. However, there was no statistically significant change in the scores of emotional aspects, mental health, and social aspects. In the intergroup comparison, only the functional capacity aspect presented statistically significant difference in exercise group when compared to orientation group.	TUG: ES = 0.32 NRS: ES = 0.25 SF36: Functional capacity: ES = 0.15 Physical Aspects: ES = 0.14 Pain: ES = 0.06 General state of health: ES = 0.05 Vitality: ES = 0.14 Social Aspects: ES = 0.22 Emotional Aspects: ES = 0.16 Mental health: ES = 0.09	Quadriceps strengthening exercises included in a rehabilitation programme are effective in the improvement of pain, function and QoL aspects of patients with knee OA.

	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
Hunt el al. (2013)	RCT	17 subjects were randomized into two groups: Exercise group (*N* = 9) or control group (*N* = 8). 16 participants completed the study (exercise group (*N* = 9) or control group (*N* = 7)).	Baseline total (*n* = 17) Age = 66.1 ± 11.3 years	All had OA in at least one knee according to the American College of Rheumatology classification criteria; reported average knee pain >3/10 on most days of the previous month; all participants had varus alignment; OA predominantly in the medial tibiofemoral	Strengthening program: 6 exercises designed to strengthen the hip abductors, hamstrings and quadriceps muscle. 3 sets of 10 reps each exercise. Exercises were performed at home and the exercise progression of resistance was monitored by a physiotherapist at weeks 1, 2, 3, 5, and 8 of the intervention. That is, 5x

TABLE 1 (Continued)

Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
		BMI = 27.0 ± 4.5 kg/m2	Compartment.	Individual treatment sessions plus home exercises 4x per week.

Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
10 weeks to minimum of 4 days per week	Biomarker assessments (urinary C-telopeptide of type II collagen (uCTX-II) and type II collagen cleavage neoepitope (uC2C), serum cartilage oligomeric matrix protein (sCOMP), serum hyaluronic acid (sHA) and serum C-propeptide of type II procollagen (sCPII));Knee joint loading during walking (walking speed; peak KAM; KAM impulse);Isometric muscle strength (isometric knee extension and flexion strength was measured using an isokinetic dynamometer; isometric hip abduction strength was measured using a handheld dynamometer)	Peak KAM was not able to explain any significant amount of variation in any biomarker or ratio when accounting for age and gender or when adding KL grade and walking speed to the models; No significant between-group differences were observed in walking speed; peak KAM; KAM impulse;When comparing changes between groups following the intervention, significantly greater reductions in sCOMP as well as slightly greater, non-significant reductions in uCTX-II were observed in the exercise group compared to those in the control group;No other significant between-group differences existed in uC2C, sHA, sCPII.No significant between-group differences were observed in knee extension torque, knee flexion torque and hip abduction torque.	Gait outcomes: Peak KAM: ES = 0.25 KAM impulse: ES = 0.24 Walking speed: ES = 0.58 Strength outcomes: Knee extension torque: ES = 0.51 Knee flexion torque: ES = 0.45 Hip abduction torque: ES = 0.38 Urinary markers uCTX-II: ES = 0.5 uC2C: ES = 0.1 Serum markers sHA: ES = 0.43 sCOMP: ES = 0.54 sCPII: ES = 0.27	This study provides initial evidence of a potential relationship between loadings in the knee joint during walking and circulating levels of biomarkers associated with articular cartilage degradation, specifically uCTX-II. A beneficial effect of strengthening exercises on cartilage health as evidenced by reduced levels of circulating sCOMP was also concluded from the results, though the mechanism of this finding is unknown.

	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
Mazloum (2018)	RCT	49 subjects were randomly allocated into: Pilates (*N* = 17); conventional therapeutic exercise (*N* = 16);Control group (*N* = 16). 41 subjects completed the study (Pilates (*N* = 14); conventional therapeutic exercise (*N* = 14); control group (*N* = 13)). Male = 28 and Female = 13.	Pilates (*n* = 14) Age = 55.0 ± 8.2 years Height = 172.3 ± 6.5 cm Weight = 79.6 ± 7.1 Kg Conventional therapeutic exercise (*n* = 14) Age = 50.3 ± 8.3 years Height = 171.9 ± 6.4 cm Weight = 78.6 ± 6.3 Kg Control group (*n* = 13) Age = 50.8 ± 9.9 years Height = 174.2 ± 7.2 cm	Age over 40 years; knee pain on most days of the previous month (mean ≥ 4); osteophyte in radiography.	Pilates: 1 h for each session, including 10 min of warm-up, 40min for pilates exercises (with a gradual increase from 20 min) and 10 min for cool-down. The number of repetitions was started from 5 time and was gradually increased according to the patient's ability.The exercises integrated in the protocol: Hundred; one leg stretch; double leg stretch; Clam; Shoulder Bridge; hip Twist; Scissors; Side Kick and one leg Circle.The subjects in the conventional therapeutic exercise group followed their own specific intervention. The time was set from 30 min and increased to 60 min.The conventional therapeutic exercise

(Continues)

TABLE 1 (Continued)

	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
			Weight = 82.7 ± 7.3 Kg		included: Buttock squeeze (holding the contraction for 5 s of 5 repetitions); Buttock rock (holding the contraction for 10 s of 5 repetitions); Rock and stand (5 reps); half squat (3sets of 5 repetitions); stretching (3 sets of 30s); standing balance (5 reps); home exercise programme (three times in a day, 3 sets of 30 s).

Programme duration/ frequency	Outcome measurement	Outcomes	Effect Sizes	Conclusion
8 weeks–3 days a week	Target angel reproduction error (joint position sense);Functional performance (walking for 15 m, standing up a chair and walking for 15 m, going up and down 11 stairs);Lequesne index (evaluation of pain intensity and disability);	Significant improvement was found in the results of pain and disability between the two experimental groups compared to the control, although the patients that followed the pilates-based therapeutic programme gained more significant improvement than those that completed conventional therapeutic exercise.The time required to do functional performance, significantly decreased in both experimental groups in comparison to the subjects in the control group. However, no significant difference was detected between the experimental groups in this factor. Significant difference was found in changes of target angle reproduction error between the three groups. Although there was no significant difference between the two experimental groups.	Pilates versus control Subjective assessment of pain & disability: ES = 0.5 Objective assessment of functional performance: ES = 0.65 Target angel reproduction error: ES = 0.81 Conventional therapeutic exercise versus control Subjective assessment of pain & disability: ES = 0.35 Objective assessment of functional performance: ES = 0.72 Target angel reproduction error: ES = 0.86 Pilates versus conventional therapeutic exercise Subjective assessment of pain and disability: ES = 0.18 Objective assessment of functional performance: ES = 0.09 Target angel reproduction error: ES = 0.29	It seems that pilates training protocol can be beneficial to improve functional performance, pain, disability and knee joint position sense in patients with knee OA and involved in the rehabilitation programme along with other therapeutic exercises as a safe and efficient method.

	Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
Braghin et al. (2018)	RCT	42 Subjects were divided into three groups: Group 1 (*n* = 15), symptomatic knee OA;Group 2 (*n* = 11), asymptomatic knee OA; and Group 3, control group	Group 1: Age = 59.42 ± 8.06 years Height = 1.62 ± 0.09 m	Individuals with OA classified as Kellgren–Lawrence scale 1, 2 or 3.	The groups 1 and 2 underwent a supervised protocol consisted of: warm-up (10 min) with active movements of the upper limbs and

TABLE 1 (Continued)

Type of study	Sample (*n*)	Sample profile	Criteria	Exercise programme
	(*n* = 16). Male = 11 and Female = 31.	Weight = 78.92 ± 12.41 Kg BMI = 30.21 ± 4.63 kg/m2 Group 2: Age = 65 ± 5.06 years Height = 1.63 ± 0.08 m Weight = 73.82 ± 16.36 kg BMI = 27.67 ± 4.13 kg/m2 Group 3: Age = 60.19 ± 9.28 years Height = 1.59 ± 0.09 m Weight = 78.44 ± 17.25 kg BMI = 31.10 ± 6.96 kg/m^2		lower limbs and stretching the lower limbs; strengthening exercises for the lower limbs (20 min) with 3 sets of 15 repetitions of straight leg raises; knee flexion in a standing position; 10 repetitions of 5 s isometry of the quadriceps at 0°–30°; aerobic exercise on a stationary bicycle (20 min), starting at 65%–70% and increasing to 85%–90% of maximum heart rate in the fifth week; and stretching (5 min). The total session time in the first stage was 50 min. Beginning with the fifth session, the protocol was increased by 10min due to the inclusion of functional training, which consisted of sitting and standing from a low chair (3 sets of 10 repetitions); circuit (10 times) walking while changing direction, walking with transposition of 4 obstacles; walking on a thin mattress; balance training with one leg support; and balance board support (bipedal, 5 repetitions of 30 s). Strengthening exercises began with a 30% load of 1 RM and over 5 weeks, the load was increased to 70% of 1 RM.

Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
50–60 min, 2x/week, for 8 weeks	WOMACQuestionnaire about fallsSemi-static balanceStep up/over	In the intragroup analysis of the WOMAC questionnaire, the asymptomatic group and the control group showed no significant difference after 8 weeks of intervention, and the symptomatic group showed significantly lower values for pain and functionality;The control and symptomatic groups showed significant differences in post-intervention compared to the asymptomatic group on the pain domain, both showing higher results, although the control group showed even higher results than the	Symptomatic VS control WOMAC Total: 0.26 Pain: 0.34 Stiffness: 0.22 Function: 0.21 Step up/over: Lift-up index left: 0.2 Lift-up index Right: 0.12	After the intervention, the symptomatic group reported improvement in pain and function on the WOMAC, while the asymptomatic group showed improvement in performance in the Step Up/Over test. There were no new episodes of falls in groups 1 and 2.

(Continues)

TABLE 1 (Continued)

Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
		symptomatic group.In the Step Up/Over test, there was a significant intragroup difference only in the asymptomatic group, in the variable of movement time on the right limb, with a decrease in time after the 8-weeks intervention. There was no statistical difference in the intergroup analysis.In intragroup analysis on the semi-static balance test, the asymptomatic group showed a significant increase in postural sway in the EOSS condition after the intervention. There was no significant difference in the intergroup analysis.In the questionnaire of fall, the descriptive analyses showed clinically significant results for the groups that received intervention compared to the control group.	Movement time –Left: 0.21 Movement time – Right: 0.21 Impact index left: 0.01 Impact index Right: 0.18 Semi-static balance: Eyes-open stable surface: 0.27 Eyes-closed stable surface: 0.15 Eyes-open unstable surface (on foam): 0.12 Eyes-closed unstable surface: 0.25 Asymptomatic VS control WOMAC Total: 0.39 Pain: 0.52 Stiffness: 0.22 Function: 0.35 Step up/over: Lift-up index left: 0.36 Lift-up index Right: 0.27 Movement time –Left: 0.21 Movement time – Right: 0.29 Impact index left: 0.17 Impact index Right: 0.09 Semi-static balance: Eyes-open stable surface: 0.28 Eyes-closed stable surface: 0.03 Eyes-open unstable surface (on foam): 0.06 Eyes-closed unstable surface: 0.12	

TABLE 1 (Continued)

Programme duration/frequency	Outcome measurement	Outcomes	Effect sizes	Conclusion
			Asymptomatic VS symptomatic	
			WOMAC	
			Total: 0.36	
			Pain: 0.5	
			Stiffness: 0.04	
			Function:0.31	
			Step up/over:	
			Lift-up index left: 0.21	
			Lift-up index Right: 0.2	
			Movement time –Left: 0.01	
			Movement time – Right: 0.17	
			Impact index left: 0.23	
			Impact index	
			Right: 0.35	
			Semi-static balance:	
			Eyes-open stable surface: 0.05	
			Eyes-closed stable surface: 0.11	
			Eyes-open unstable surface (on foam): 0.17	
			Eyes-closed unstable surface: 0.14	

Abbreviations: ABC Scale: Activities-Specific Balance Confidence Scale; ACR, American College of Rheumatology; BDI, Beck Depression Inventory; BMI, body mass index; CNC RT, concentrically based resistance exercise training programme; ECC RT, eccentrically based resistance exercise training programme; ES, effect size; FAB scale: Fullerton Advanced Balance; KOOS, Knee Injury and Osteoarthritis Outcome Score; NRS: Numeric Rating Scale; OA, osteoarthritis; QoL, quality of life; RCT, randomized controlled trial; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

knee extension, knee flexion and leg press (Vincent et al., 2019) were the tests performed.

Balance was evaluated through four different scales: Berg Balance Scale (Simão et al., 2012); Activities-Specific Balance Confidence (ABC) scale and Fullerton Advanced Balance (FAB) scale (Shellington et al., 2019); Balance Master System and modified Clinical Test of Sensory Interaction and Balance (Braghin et al., 2018).

Furthermore, two studies measured the proprioception using a platform which was moved by an electric motor (Lai et al., 2018) and the Biodex system, evaluating the joint position sense (Mazloum et al., 2018). One study assessed ROM with a goniometer (Wang et al., 2011).

3.6 | Duration and frequency of the program

The studies included in this review present exercise programmes whose duration varied from 4 (Karadağ et al., 2019) to 24 weeks (Shellington et al., 2019). The majority of them lasted 12 weeks ($n = 7$) (DeVita et al., 2018; Ha et al., 2018; Henriksen et al., 2014; Huang et al., 2020; Liu et al., 2019; Simão et al., 2012; Wang et al., 2011) or 8 weeks ($n = 6$) (Braghin et al., 2018; de Oliveira et al., 2012; de Oliveira et al., 2012; Lai et al., 2018; Mazloum et al., 2018; Silva et al., 2015). The frequency of the training sessions varied from two (Braghin et al., 2018; de Oliveira et al., 2012; Dias et al., 2017; Imoto et al., 2012; Shellington et al., 2019; Silva et al., 2015; Vincent et al., 2019) to five times (Silva et al., Karadağ et al., 2019; Liu et al., 2019) per week. The longest session found in all studies was 1 h (DeVita et al., 2018; Ha et al., 2018; Henriksen et al., 2014; Huang et al., 2020; Liu et al., 2019; Mazloum et al., 2018; Munukka et al., 2016; Shellington et al., 2019; Silva et al., 2015; Wang et al., 2011) and the shortest one varied from 12 (Lai et al., 2018) to 20 min (Karadağ et al., 2019), considering the fact that the 12-min session turned out to be 39 min at the end of that programme due to progression. Four studies didn't specify the time spent on the exercise session (Braghin et al., 2018; de Oliveira et al., 2012; Simão et al., 2012; Vincent et al., 2019).

3.7 | Type of exercise

Strengthening ($n = 15$) and aerobic exercise ($n = 11$) were the most common types of exercise found in the retrieved studies.

Strengthening land-based programmes involved many different strategies of exercise.

In two RCTs, a strength circuit training was applied: one with free weights, elastic rubber bands, or body weight as resistance (Henriksen et al., 2014) and another one with hydraulic resistance machines like chest press/row, biceps curl/triceps extension, upright row/press, ab/back, hip abduction/adduction, leg press/curl, and leg extension/curl (Huang et al., 2020). Other study also involved resistance training in those machines, with a resistance load of 60% of the concentric 1 RM, performing one set of 8–12 repetitions (Vincent et al., 2019).

Ten studies integrated a strength exercise programme of the lower limbs, which involved exercises such as squat, leg press, forward lunges, straight leg raises, and others involving knee extension, hip abduction, hamstrings, gluteus and hip adductors (Braghin et al., 2018; de Oliveira et al., 2012; DeVita et al., 2018; Hunt et al., 2013; Imoto et al., 2012; Karadağ et al., 2019; Lai et al., 2018; Mazloum et al., 2018; Silva et al., 2015; Simão et al., 2012). The majority of the studies included the execution of three sets of these exercises (Braghin et al., 2018; de Oliveira et al., 2012; DeVita et al., 2018; Hunt et al., 2013; Imoto et al., 2012) and the number of repetitions varied from 10 (DeVita et al., 2018; Hunt et al., 2013) to 15 (Braghin et al., 2018; de Oliveira et al., 2012; Imoto et al., 2012).

Moreover, the most common form of aerobic land-based exercise found on these studies was stationary bicycle (Braghin et al., 2018; de Oliveira et al., 2012; Henriksen et al., 2014; Imoto et al., 2012; Liu et al., 2019; Silva et al., 2015; Simão et al., 2012). Two studies fail to specify the form of exercise performed (DeVita et al., 2018; Huang et al., 2020) and another one involved different forms of walking and lower and upper limb movement (Wang et al., 2011). Of the studies whose duration of aerobic exercise is known, the minimum was 5 min (Silva et al., 2015) and the maximum 20 (Braghin et al., 2018).

From all the 19 studies, 4 comprehended aquatic programmes (Dias et al., 2017; Ha et al., 2018; Munukka et al., 2016; Wang et al., 2011). Of those four, one presented only a type of exercise—strengthening training (Munukka et al., 2016). The other three RCTs offered a combination of exercises, with stretching/flexibility being common to all (Dias et al., 2017; Ha et al., 2018; Wang et al., 2011). One included aerobic training (Wang et al., 2011), other included aerobic and plyometric training (Ha et al., 2018), and another one included strengthening training too, consisting of closed kinetic chain exercises using float as well as multidirectional walking tasks (Dias et al., 2017).

Pilates training was only approached in 1 of the 19 studies, with a 1-h programme which included 40 min of Pilates exercises like the Hundred, One Leg Stretch, Double Leg Stretch, Clam, Shoulder Bridge, Hip Twist, Scissors, Side Kick and One Leg Circle (Mazloum et al., 2018).

Five RCTs mentioned that the intervention group not only received the exercise therapy but also education (de Oliveira et al., 2012; Dias et al., 2017; Huang et al., 2020; Imoto et al., 2012; Silva et al., 2015).

3.8 | Comparisons and outcome

All of the studies compared an exercise programme against no intervention. When comparing the results, all studies reported improvement in at least one of the variables measured, except one which failed to find any significant improvement related to physical and functional outcomes analysed in our study (Hunt et al., 2013).

3.8.1 | Pain, PPTs and TSs

From 15 studies that measured pain, 10 RCTs found a significant improvement on this parameter (ES between 0.06 and 1.2) (de Oliveira et al., 2012; DeVita et al., 2018; Dias et al., 2017; Henriksen et al., 2014; Imoto et al., 2012; Liu et al., 2019; Mazloum et al., 2018; Silva et al., 2015; Simão et al., 2012; Wang et al., 2011). One of those studies also revealed that the patients that followed the Pilates-based therapeutic programme gained more significant improvement than those that completed conventional therapeutic exercise (CTE) (Mazloum et al., 2018).

One of the studies mentioned above revealed significant difference when comparing the control with the aquatic and the land-based group, yet no difference was found when comparing the two intervention groups (Wang et al., 2011). Other RCT also found significant differences between platform and control groups, but no statistically significant differences were found between control and squat groups (Simão et al., 2012).

In some other studies, there was also improvement of pain, but it wasn't considered statistically significant (Ha et al., 2018; Karadağ et al., 2019; Shellington et al., 2019; Vincent et al., 2019). However, one study revealed greater improvement in the exercise group comparing to the exercise after heat application group (Karadağ et al., 2019).

Moreover, other study showed that a supervised exercise programme reduced the pressure–pain sensitivity (ES = 0.62) and TS (ES = 0.62) compared to a no-attention control group, adding an effect on self-reported pain (ES = 0.71) (Henriksen et al., 2014).

Another study compared a control group with two intervention groups (one symptomatic and other asymptomatic), and it showed significant differences in post-intervention comparing the control and the symptomatic groups to the asymptomatic one. Both control and symptomatic groups presented higher results on pain, although the control group showed even higher results (Braghin et al., 2018).

3.8.2 | Function

From 15 studies measuring function, 9 presented no significant differences between the control and the intervention(s) groups (Braghin et al., 2018; Henriksen et al., 2014; Karadağ et al., 2019; Liu et al., 2019; Munukka et al., 2016; Shellington et al., 2019; Simão et al., 2012; Vincent et al., 2019; Wang et al., 2011) and 7 showed statistically significant results (ES between 0.1 and 1 or above) (de Oliveira et al., 2012; DeVita et al., 2018; Dias et al., 2017; Ha et al., 2018; Mazloum et al., 2018; Silva et al., 2015; Wang et al., 2011). From those studies, one is coincident since it showed statistically significant group-by-time interactions in sport/recreation function (ES = 0.30) but not in ADL function, except in the land-based group at 12 weeks of programme (ES = 0.2) (Wang et al., 2011). Also, one of those studies also revealed that the patients that followed the Pilates-based therapeutic programme gained more significant improvement than those that completed CTE (Mazloum et al., 2018).

3.8.3 | Functional performance

When it comes to evaluation of functional performance, 10 RCTs had mostly found positive results.

Concerning 6MWT, while one study didn't show positive results (Shellington et al., 2019), three other studies found significant post intervention improvements (ES between 0.15 and 0.38) (Silva et al., 2015; Simão et al., 2012; Wang et al., 2011). One of those RCTs only showed improvements in the platform squat group (Simão et al., 2012).

Four studies involved TUG assessment (de Oliveira et al., 2012; Imoto et al., 2012; Shellington et al., 2019; Silva et al., 2015) and three of them found statistically significant differences (ES = 0.32–0.6) (de Oliveira et al., 2012; Imoto et al., 2012; Silva et al., 2015).

Regarding Chair-Stand, only one of the two studies (Shellington et al., 2019; Silva et al., 2015) found positive results (ES = 0.43) (Silva et al., 2015).

Regarding walking velocity, two studies found significant post intervention improvements using tridimensional motion analysis system (ES = 0.98) (DeVita et al., 2018) and Gait Speed Test (ES = 0.02) (Simão et al., 2012), but one failed to achieve significant results (Hunt et al., 2013). Moreover, one of these studies found that the gait speed in the platform group was faster than in the squat group after training (ES = 0.02) (Simão et al., 2012).

Walking for 15 m, standing up a chair and walking for 15 m, and going up and down 11 stairs also revealed significant post-intervention improvements (Pilates: ES = 0.65; CTE = 0.72). However, between those two experimental groups, no significant difference was detected (Mazloum et al., 2018).

On the other hand, no significant differences were found for Sit-and-Reach (Silva et al., 2015), STEP-TEST (Shellington et al., 2019) and Step Up/Over tests (Braghin et al., 2018).

3.8.4 | Quality of life

Six studies evaluated QoL and three of them, measuring it through KOOS, found no significant post-intervention improvements (Henriksen et al., 2014; Liu et al., 2019; Munukka et al., 2016). The remaining three RCTs revealed significant post-intervention improvements in KOOS (Wang et al., 2011) and SF-36 (Imoto et al., 2012; Silva et al., 2015). Relatively to this last instrument, one study showed improvements in all domains (ES = 0.35 – 0.64), except mental health and social function (Silva et al., 2015) and the other one only showed a statistically significant result in functional capacity domain (ES = 0.15) (Imoto et al., 2012).

3.8.5 | Range of motion

Only one study measured ROM and it showed statistically significant improvements in knee extension (ES between 0.25 and 0.45) and knee flexion (ES between 0.22 and 0.26) in both intervention groups (Wang et al., 2011).

3.8.6 | Strength

Concerning strength evaluation, the study including 1RM showed improvement for all leg strength measures, comparing to the control group (Vincent et al., 2019). Additionally, when comparing both intervention groups with each other, the rate of weekly strength gain was greater for the concentric exercise group than for the eccentric exercise group, for leg press and knee flexion, but not for knee extension. However, at the end of the study, the difference between those two groups was not statistically significant (Vincent et al., 2019).

Concerning isokinetic evaluation, the results were variable. Statistically significant results were found in knee extensor muscles function (Ha et al., 2018), strength (DeVita et al., 2018; Dias et al., 2017) and resistance (Dias et al., 2017) (ES between 0.27 and 0.32, ES = 0.08, and ES = 0.17, respectively); in knee flexors strength and power (ES = 0.14 and ES = 0.01, respectively); and in the difference score for maximum negative quadriceps power (ES = 0.91) (DeVita et al., 2018).

No significant difference was found for knee flexor function (Ha et al., 2018), resistance and for knee extensors power (Dias et al., 2017); for hip abduction torque, knee extension torque, knee flexion torque (Hunt et al., 2013) and knee internal extension torque during loading phase (DeVita et al., 2018); for peak knee adduction moment (KAM) and KAM impulse (Hunt et al., 2013); for maximum quadriceps force and maximum compressive knee force during walking, for negative quadriceps work and maximum positive quadriceps power and work in early stance (DeVita et al., 2018).

3.8.7 | Proprioception

Two studies measured the proprioception using a platform which was moved by an electric motor (Lai et al., 2018) and using the Biodex system, evaluating the joint position sense (Mazloum et al., 2018). There were significant improvements demonstrated by changes of target angle reproduction error (ES between 0.81 and 0.86), but between the two experimental groups (Pilates and CTE), there was no significant difference (Mazloum et al., 2018). A significant improvement of passive motion sense in knee flexion was also detected (ES = 0.124). However, no significant differences of passive motion senses were found in knee extension and ankle (Lai et al., 2018).

3.8.8 | Balance

Three studies (Braghin et al., 2018; Shellington et al., 2019; Simão et al., 2012) assessed balance and only one demonstrated statistically significant improvements (Simão et al., 2012).

4 | DISCUSSION

Overall, the results suggest a positive effect of exercise in the reviewed studies for at least one outcome variable. Moreover, exercise seems to be an effective way of managing knee OA, bringing positive physical and functional outcomes.

Pain was one of the most studied variables in all the retrieved RCTs presenting significant improvement. Associated to this outcome, one study included in this review found reduced pressure–pain sensitivity and TS. The existing evidence supports that pain sensitivity and temporal summation have been found to be diminished following exercise, in line with the development of hypoalgesia (Koltyn, Brellenthin, Cook, Sehga, & Hillard, 2018; Vaegter, Handberg, & Graven-Nielsen, 2015). Some previous reviews identified evidence supporting the role of exercise in pain decrease in knee OA patients (Bartels et al., 2016; Bartholdy et al., 2017; Fransen et al., 2015; McAlindon et al., 2014).

Concerning function, the results showed some controversy. However, the studies that found positive results presented a medium to high ES, revealing some clinical significance.

Functional performance showed mostly positive results in 6MWT and TUG, although its ES were low to medium. Walking for 15 m, going up and down 11 stairs, and standing up a chair and walking for 15 m also presented significant improvements. Tests such as Sit-and-reach, STEP-TEST and Step Up/Over test didn't reach to the same results. Despite the tendency suggesting positive results for functional performance after exercise programmes, different outcome measures in the retrieved studies enables the general statement. A systematic review assessing the effect of a water-based programme, using TUG and tests that measure the time to cover a certain distance, report that this type of exercise programme improves functional performance (Mattos, Leite, Pitta, & Bento, 2016). Along with others, our review suggests exercise to be efficient in improving functional performance in knee OA patients.

Despite the existence of evidence supporting the use of exercise to improve QoL (Fransen et al., 2015), retrieved studies assessing QoL, using SF-36 and KOOS, were inconclusive as three studies found improvements against no improvements in the remaining three. The conflicting results found in our review may be related to the use of two different QoL measurement tools. While SF-36 is a generic health status instrument (Tanaka, Ozawa, Kito, & Moriyama, 2015), KOOS is a feasible and validated tool for assessment of knee OA (Roos & Lohmander, 2003). The methods applied to patient's blinding in the studies which found no improvement suggest the possibility of bias to the results and may substantiate another hypothesis to explain the differences between our results and the literature.

Most studies, assessing strength, found positive results in at least one of the strength's components. Relatively to knee flexors, there was improvement in strength and power. Concerning knee extensors,

function, strength and resistance were the variables presenting positive results. Despite the results those improvements revealed low ES and more studies measuring strength are required to build more consistent evidence.

Both studies assessing proprioception showed significant improvements; however, more studies are required to assess that outcome in knee OA patients going through an exercise programme.

The studies included showed significant improvements in ROM yet, significant results were found concerning balance. As the number of studies assessing these variables were very limited, more studies are needed to build consistent evidence in all these matters.

Concerning our secondary objective of identifying the best intervention to provide both healthcare professionals and knee OA patients with updated and high-quality recommendations for the management of OA, it is possible to critically extrapolate the literature to clinical practice.

From those studies which showed significant improvement on pain, stationary cycling was the type of exercise that revealed the higher ES (ES = 1.2), with a frequency of 5 days a week, for 12 weeks, each session lasting 1 h. Other types of exercise such as combination of 10-min aerobic warm-up, varying from stationary bicycle to treadmill, followed by strengthening of the trunk and lower limbs also presented significant improvements and medium to high ES (ES from 0.71 to >1). Moreover, 10-min warm-up, 40-min Pilates training and 10-min cool down also presented positive effects with a medium ES of 0.5. Additionally, that Pilates programme and aerobic warm-up, and quadriceps strengthening programmes also proved to be effective regarding function improvement, with ES of 0.5 and >1, respectively. Based on our results, the authors suggest an intervention of these types of exercise consisting of 1h session, 3–5 days a week, for 8–12 weeks, for positive results in pain and/or function improvement. Other authors who also studied the effect of a strengthening and aerobic exercise verified that it could significantly relieve knee OA joint pain and improve physical function (Bartels et al., 2016; Bartholdy et al., 2017; Dong et al., 2018; Fransen et al., 2015; Hislop et al., 2020; Jeong et al., 2019; McAlindon et al., 2014). For strength improvement, our results defend an implementation of a 6–16-week exercise programme, with 2–3 sessions per week of land-based or aquatic strengthening training.

Because of the water temperature, decreased loading and hydrostatic pressure, aquatic exercise is often considered an ideal place to begin exercise or for those in the more advanced stages of the disease where exercise on land has become too difficult (Bartels et al., 2016). Regarding aquatic programmes, through one study, the authors found the possibility that a 1h aquatic session improved significantly cardiorespiratory fitness, with an ES of 0.58. Even though this medium ES, with only one study verifying this result, one must be critical when extrapolating this data. The results of other two studies that included aquatic programmes are somehow inconclusive since different programs were applied and both presented low ES.

Summarizing our results, strengthening, aerobic and Pilates exercise seem to be effective on the treatment of knee OA patients. Similarly, both aquatic and land-based programmes show improvement on pain relief, physical function, and QoL, both in short- and long-term outcomes. Relatively to stretching, proprioception and coordination training, the authors can't take clear conclusions, besides speculating that those types of training, when combined with strength and/or aerobic exercise, may constitute a great asset. Particularly, evidence shows that, comparing to non-exercise, proprioceptive training may be more helpful for pain relief and stretching training may be beneficial for ROM and gait speed improvement (Aoki et al., 2009; Fransen et al., 2015). Programmes that include agility, coordination and balance (sensory-motor training) may be effective through exposing individuals to potentially destabilizing loads. This allows the neuromuscular system to adapt to conditions that could induce knee instability during activities of daily living, presenting significant improvement in perceived pain and performing functional tests (Gomiero et al., 2018).

Even though exercise is considered a core treatment for knee OA (NICE, 2020), education plays an important role in providing the best intervention to the patients (Ram, Booth, Thom, & Jones, 2020). Five articles included in this review comprised exercise therapy plus education, and four of them presented statistically significant improvements.

Taking into consideration all findings of our study and the literature referred above, the best intervention the physiotherapist can give will be an evidence-based and patient-centred one, respecting patient's values and needs, supplying high-quality information and education to the patient and family, providing physical comfort and emotional support (Yetzer & Disney, 2017).

Globally, the quality of the studies included in this systematic review is considered high, with a few situations in which the bias is possible in some parameters of the methodological quality assessment. Moreover, some studies included don't report ES nor data to make it possible for the authors to calculate it. Some studies which reported significant improvements presented low ES, which limits the capacity for extrapolating information to clinical practice. For those reasons, the results of this systematic review must be viewed with caution and critically. Thus, the distinct outcomes and outcome instruments prevented a meta-analysis. The lack of more studies, according to our initial criteria, evaluating variables such as balance, proprioception, leisure activities, VO_2 max and ROM, also constitute a limitation of our study and should be considered for future research works. Furthermore, in future studies, it would also be interesting to assess variables like flexibility, coordination, and even satisfaction and social participation associated with an exercise programme.

5 | CONCLUSION

Exercise programmes appear to be safe and effective in knee OA patients. Thus, there is substantial evidence regarding the effects of exercise in pain and strength improvement. Concerning the other variables in study, further studies are necessary to confirm the positive effect of exercise in its improvement.

Based on our systematic review, in order to obtain those benefits, Pilates, aerobic and strengthening exercise programmes should

be performed for 8–12 weeks, 3–5 sessions per week, each session lasting 1 h. Both aquatic and land-based exercise programmes show comparable and positive effects.

Therefore, exercise programmes may play an important role in the rehabilitation of knee OA patients.

CONFLICT OF INTEREST

The authors have no conflict of interests.

ETHICS STATEMENT

No ethical statement was required for this work.

AUTHOR CONTRIBUTIONS

Planning, guiding and overseeing: Ana Lúcia Cruz. *Development and writing*: Marta Oliveira Ramos and Filipe Jorge Bastos Raposo.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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REFERENCES

Aoki, O., Tsumura, N., Kimura, A., Okuyama, S., Takikawa, S., & Hirata, S. (2009). Home stretching exercise is effective for improving knee range of motion and gait in patients with knee osteoarthritis. *Journal of Physical Therapy Science*, *21*(2), 113–119.

Bartels, E., Juhl, C., Christensen, R., Hagen, K., Dagfinrud, H., & Lund, H. (2016). Aquatic exercise for the treatment of knee and hip osteoarthritis (Review): Summary of findings for the main comparison. *Cochrane Database of Systematic Reviews*, *3*.

Bartholdy, C., Juhl, C., Christensen, R., Lund, H., Zhang, W., & Henriksen, M. (2017). The role of muscle strengthening in exercise therapy for knee osteoarthritis: A systematic review and meta-regression analysis of randomized trials. *Seminars in Arthritis and Rheumatism*, *47*, 921.

Braghin, R. de M. B., Libardi, E. C., Junqueira, C., NogueiraBarbosa, –M. H., & de Abreu, D. C. C. (2018). Exercise on balance and function for knee osteoarthritis: A randomized controlled trial. *Journal of Bodywork and Movement Therapies [Internet]*, *22*(1), 76–82. https://doi.org/10.1016/j.jbmt.2017.04.006.

Bricca, A., Juhl, C. B., Steultjens, M., Wirth, W., & Roos, E. M. (2019). Impact of exercise on articular cartilage in people at risk of, or with established, knee osteoarthritis: A systematic review of randomised controlled trials. *British Journal of Sports Medicine*, *53*(15), 940–947.

Brosseau, L., Taki, J., Desjardins, B., Thevenot, O., Fransen, M., Wells, G. A., et al. (2017). The Ottawa panel clinical practice guidelines for the management of knee osteoarthritis. Part three: Aerobic exercise programs. *Clinical Rehabilitation*, *31*(5), 612–624.

de Oliveira, A. M. I., Peccin, M. S., da Silva, K. N. G., de Paiva Teixeira, L. E. P., & Trevisani, V. F. M. (2012). Impacto dos exercícios na capacidade funcional e dor em pacientes com osteoartrite de joelhos: Ensaio clínico randomizado. *Revista Brasileira de Reumatologia*, *52*(6), 876–882.

de Rezende, M. U., & de Campos, G. C. (2013). Is osteoarthritis a mechanical or inflammatory disease? *Revista Brasileira de Ortopedia (English Edition) [Internet]*, *48*(6), 471–474. http://dx.doi.org/10.1016/j.rboe.2013.12.002.

de Rooij, M., van der Leeden, M., Heymans, M. W., Holla, J. F. M., Häkkinen, A., Lems, W. F., et al. (2016 Mar). Course and predictors of pain and physical functioning in patients with hip osteoarthritis: Systematic review and meta-analysis. *Journal of Rehabilitation Medicine*, *48*(3), 245–252.

DeVita, P., Aaboe, J., Bartholdy, C., Leonardis, J. M., Bliddal, H., & Henriksen, M. (2018). Quadriceps-strengthening exercise and quadriceps and knee biomechanics during walking in knee osteoarthritis: A two-centre randomized controlled trial. *Clinical Biomechanics*, *59*, 199–206.

Dias, J. M., Cisneros, L., Dias, R., Fritsch, C., Gomes, W., Pereira, L, et al. (2017). Hydrotherapy improves pain and function in older women with knee osteoarthritis: A randomized controlled trial. *Brazilian Journal of Physical Therapy [Internet]*, *21*(6), 449–456. http://dx.doi.org/10.1016/j.bjpt.2017.06.012.

Dong, R., Wu, Y., Xu, S., Zhang, L., Ying, J., Jin, H, et al. (2018). Is aquatic exercise more effective than land-based exercise for knee osteoarthritis? *Medicine (Baltimore)*, *97*.

Espirito Santo, H., & Daniel, F. B. (2015). Calcular e apresentar tamanhos do efeito em trabalhos científicos (1): As limitações do p < 0,05 na análise de diferenças de médias de dois grupos. *Revista Portuguesa de Cardiologia*, *1*(1), 3–16.

Fransen, M., Mcconnell, S., Harmer, A. R., Van der Esch, M., Simic, M., & Bennell, K. L. (2015). Exercise for osteoarthritis of the knee: a Cochrane database of systematic reviews. *British Journal of Sports Medicine*, *49*(24), 1554–1557.

Gomiero, A. B., Kayo, A., Abraão, M., Peccin, M. S., Grande, A. J., & Trevisani, V. F. (2018). Sensory-motor training versus resistance training among patients with knee osteoarthritis: Randomized single-blind controlled trial. *Sao Paulo Medical Journal*, *136*(1), 44–50.

Ha, G.-C., Yoon, J.-R., Yoo, C.-G., Kang, S.-J., & Ko, K.-J. (2018 Oct). Effects of 12-week aquatic exercise on cardiorespiratory fitness, knee isokinetic function, and Western Ontario and McMaster University osteoarthritis index in patients with knee osteoarthritis women. *Journal of Exercise Rehabilitation*, *14*(5), 870–876.

Henriksen, M., Klokker, L., Graven-Nielsen, T., Bartholdy, C., Schjødt Jørgensen, T., Bandak, E, et al. (2014 Dec). Association of exercise therapy and reduction of pain sensitivity in patients with knee osteoarthritis: A randomized controlled trial. *Arthritis Care & Research*, *66*(12), 1836–1843.

Higgins, J., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M, et al. (2019). *Cochrane handbook for systematic reviews of interventions*.

Hislop, A. C., Collins, N. J., Tucker, K., Deasy, M., & Semciw, A. I. (2020). Does adding hip exercises to quadriceps exercises result in superior outcomes in pain, function and quality of life for people with knee osteoarthritis? A systematic review and meta-analysis. *British Journal of Sports Medicine*, *54*(5), 263–271.

Huang, C. C., Wang, H. H., Chen, K. C., Yang, K. J., Chang, L. Y., Shiang, T. Y, et al. (2020). Effects of a dynamic combined training on impulse response for middle-aged and elderly patients with osteoporosis and knee osteoarthritis: A randomized control trial. *Aging Clinical and Experimental Research [Internet]*. https://doi.org/10.1007/s40520-020-01508-0.

Huang, L., Guo, B., Xu, F., & Zhao, J. (2018). Effects of quadriceps functional exercise with isometric contraction in the treatment of knee osteoarthritis. *International Journal of Rheumatic Diseases*, *21*(5), 952–959.

Hunt, M. A., Pollock, C. L., Kraus, V. B., Saxne, T., Peters, S., Huebner, J. L., Sayre, E.C., & Cibere, J., et al. (2013 Mar). Relationships amongst osteoarthritis biomarkers, dynamic knee joint load, and exercise: Results from a randomized controlled pilot study. *BMC Musculoskeletal Disorders*, *14*, 115.

Imoto, A. M., Peccin, M. S., & Trevisani, V. F. M. (2012). Quadriceps strengthening exercises are effective in improving pain, function and quality of life in patients with osteoarthritis of the knee. *Acta Ortopédica Brasileira*, *20*(3), 174–179.

Jeong, H. S., Lee, S.-C., Jee, H., Song, J. B., Chang, H. S., & Lee, S. Y. (2019). Proprioceptive training and outcomes of patients with knee osteoarthritis: A meta-analysis of randomized controlled trials. *Journal of Athletic Training*, *54*(4), 418–428.

Karadağ, S., Taşci, S., Doğan, N., Demir, H., & Kiliç, Z. (2019). Application of heat and a home exercise program for pain and function levels in patients with knee osteoarthritis: A randomized controlled trial. *International Journal of Nursing Practice*, *25*, e12772.

Kolasinski, S. L., Neogi, T., Hochberg, M. C., Oatis, C., Guyatt, G., Block, J, et al. (2019). American College of rheumatology/arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care & Research*, *72*(2), 149–162.

Koltyn, K. F., Brellenthin, A. G., Cook, D., Sehga, N., & Hillard, C. (2018). Mechanisms of exercise-induced hypoalgesia. *Psychiatrie*, *22*(1), 33–38.

Kus, G., & Yeldan, I. (2019). Strengthening the quadriceps femoris muscle versus other knee training programs for the treatment of knee osteoarthritis. *Rheumatology International*, *39*(2), 203–218.

Lai, Z., Zhang, Y., Lee, S., & Wang, L. (2018). Effects of strength exercise on the knee and ankle proprioception of individuals with knee osteoarthritis. *Research in Sports Medicine*, *26*(2), 138–146.

Liu, J., Chen, L., Chen, X., Hu, K., Tu, Y., Lin, M, et al. (2019). Modulatory effects of different exercise modalities on the functional connectivity of the periaqueductal grey and ventral tegmental area in patients with knee osteoarthritis: A randomised multimodal magnetic resonance imaging study. *British Journal of Anaesthesia*, *123*(4), 506–518.

Lu, M., Su, Y., Zhang, Y., Zhang, Z., Wang, W., He, Z, et al. (2015). Effectiveness of aquatic exercise for treatment of knee osteoarthritis: Systematic review and meta-analysis. *Zeitschrift für Rheumatologie*, *74*(6), 543–552.

Mattos, F., Leite, N., Pitta, A., & Bento, P. C. B. (2016). Effects of aquatic exercise on muscle strength and functional performance of individuals with osteoarthritis: A systematic review. *Revista Brasileira de Reumatologia (English Ed [Internet]*, *56*(6), 530–542. http://dx.doi.org/10.1016/j.rbre.2016.09.003.

Mazloum, V., Rabiei, P., Rahnama, N., & Sabzehparvar, E. (2018). The comparison of the effectiveness of conventional therapeutic exercises and Pilates on pain and function in patients with knee osteoarthritis. *Complementary Therapies in Clinical Practice [Internet]*, *31* 343–348. https://doi.org/10.1016/j.ctcp.2017.10.008.

McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M., et al. (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis and Cartilage [Internet]*, *22*(3), 363–388. http://dx.doi.org/10.1016/j.joca.2014.01.003.

Munukka, M., Waller, B., Rantalainen, T., Häkkinen, A., Nieminen, M. T., Lammentausta, E, et al. (2016). Efficacy of progressive aquatic resistance training for tibiofemoral cartilage in postmenopausal women with mild knee osteoarthritis: A randomised controlled trial. *Osteoarthritis and Cartilage*, *24*(10), 1708–1717.

NICE (2020). *Osteoarthritis : Care and management. NICE Guide l [Internet]*, pp.1–30. https://www.nice.org.uk/guidance/cg177/resources/osteoarthritis-care-and-management-pdf-35109757272517.

O'Neill, T. W., McCabe, P. S., & McBeth, J. (2018). Update on the epidemiology, risk factors and disease outcomes of osteoarthritis. *Best Practice & Research: Clinical Rheumatology [Internet]*, *32*(2), 312–326. https://doi.org/10.1016/j.berh.2018.10.007.

Palazzo, C., Nguyen, C., Lefevre-Colau, M. M., Rannou, F., & Poiraudeau, S. (2016). Risk factors and burden of osteoarthritis. *Annals of Physical and Rehabilitation Medicine*, *59*(3), 134–138.

Ram, A., Booth, J., Thom, J., & Jones, M. D. (2020). Exercise and education for knee osteoarthritis—what are accredited exercise physiologists providing? *Musculoskeletal Care*. *18*(4), 425–433.

Roos, E., & Lohmander, L. S. (2003). The knee injury and osteoarthritis outcome score (KOOS): From joint injury to osteoarthritis. *BioMed Central*, *1*(64).

Sandell, L., & Aigner, T. (2001). Articular cartilage and changes in arthritis an introduction: Cell biology of osteoarthritis. *Arthritis Research*, *3*(6), 337–341.

Shellington, E. M., Gill, D. P., Shigematsu, R., & Petrella, R. J. (2019). Innovative exercise as an intervention for older adults with knee osteoarthritis: A pilot Feasibility study. *Canadian Journal on Aging*, *38*(1), 111–121.

Silva, F., de Melo, F. E. S., do Amaral, M. M. G., Caldas, V. V. A., Pinheiro, ÍL. D., Abreu, B. J., et al. (2015). Efficacy of simple integrated group rehabilitation program for patients with knee osteoarthritis: Single-blind randomized controlled trial. *Journal of Rehabilitation Research and Development*, *52*(3), 309–322.

Simão, A. P., Avelar, N. C., Tossige-Gomes, R., Neves, C. D., Mendonça, V. A., Miranda, A. S, et al. (2012 Oct). Functional performance and inflammatory cytokines after squat exercises and whole-body vibration in elderly individuals with knee osteoarthritis. *Archives of Physical Medicine and Rehabilitation*, *93*(10), 1692–1700.

Tanaka, R., Ozawa, J., Kito, N., & Moriyama, H. (2014). Effect of the frequency and duration of land-based therapeutic exercise on pain relief for people with knee osteoarthritis: A systematic review and meta-analysis of randomized controlled trials. *Journal of Physical Therapy Science*, *26*(7), 969–975.

Tanaka, R., Ozawa, J., Kito, N., & Moriyama, H. (2015). Does exercise therapy improve the health-related quality of life of people with knee osteoarthritis? A systematic review and meta-analysis of randomized controlled trials. *Journal of Physical Therapy Science*, *27*(10), 3309–3314.

Vaegter, H. B., Handberg, G., & Graven-Nielsen, T. (2015). Isometric exercises reduce temporal summation of pressure pain in humans. *European Journal of Pain*, *19*(7), 973–983.

Van Ginckel, A., Hall, M., Dobson, F., & Calders, P. (2019). Effects of long-term exercise therapy on knee joint structure in people with knee osteoarthritis: A systematic review and meta-analysis. *Seminars in Arthritis and Rheumatism [Internet]*, *48*(6), 941–949 https://doi.org/10.1016/j.semarthrit.2018.10.014

Vincent, K. R., Vasilopoulos, T., Montero, C., & Vincent, H. K. (2019). Eccentric and concentric resistance exercise comparison for knee osteoarthritis. *Medicine & Science in Sports & Exercise*, *51*(10), 1977–1986.

Wang, T.-J., Lee, S.-C., Liang, S.-Y., Tung, H.-H., Wu, S.-F. V., & Lin, Y.-P. (2011 Sep). Comparing the efficacy of aquatic exercises and land-based exercises for patients with knee osteoarthritis. *Journal of Clinical Nursing*, *20*(17–18), 2609–2622.

Yetzer, T., & Disney, H. (2017). A biopsychosocial approach in physical therapy to treat a patient with chronic osteoarthritic associated knee pain. *Trends in Medicine*, *17*(1), 1–5.

Zampogna, B., Papalia, R., Papalia, G. F., Campi, S., Vasta, S., Vorini, F, et al. (2020 Apr). The role of physical activity as conservative treatment for hip and knee osteoarthritis in older people: A systematic review and meta-analysis. *Journal of Clinical Medicine*, *9*(4).

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APPENDIX

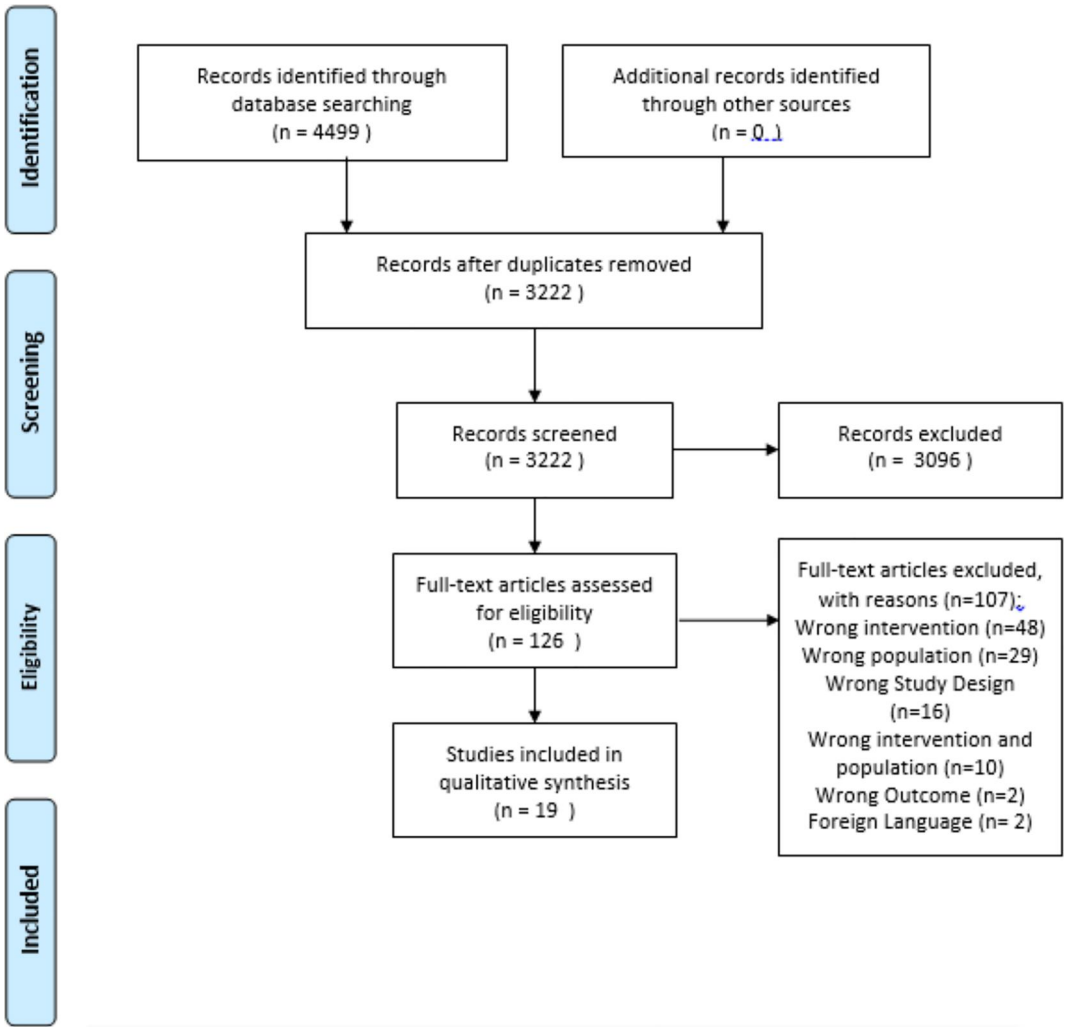

FIGURE A1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram

FIGURE A2 Risk of bias assessment

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Osteoarthritis and Cartilage

OARSI guidelines for the non-surgical management of knee osteoarthritis

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SUMMARY

Objective: To develop concise, up-to-date, patient-focused, evidence-based, expert consensus guidelines for the management of knee osteoarthritis (OA), intended to inform patients, physicians, and allied healthcare professionals worldwide.

Method: Thirteen experts from relevant medical disciplines (primary care, rheumatology, orthopedics, physical therapy, physical medicine and rehabilitation, and evidence-based medicine), three continents and ten countries (USA, UK, France, Netherlands, Belgium, Sweden, Denmark, Australia, Japan, and Canada) and a patient representative comprised the Osteoarthritis Guidelines Development Group (OAGDG). Based on previous OA guidelines and a systematic review of the OA literature, 29 treatment modalities were considered for recommendation. Evidence published subsequent to the 2010 OARSI guidelines was based on a systematic review conducted by the OA Research Society International (OARSI) evidence team at Tufts Medical Center, Boston, USA. Medline, EMBASE, Google Scholar, Web of Science, and the Cochrane Central Register of Controlled Trials were initially searched in first quarter 2012 and last searched in March 2013. Included evidence was assessed for quality using Assessment of Multiple Systematic Reviews (AMSTAR) criteria, and published criticism of included evidence was also considered. To provide recommendations for individuals with a range of health profiles and OA burden, treatment recommendations were stratified into four clinical sub-phenotypes. Consensus recommendations were produced using the RAND/UCLA Appropriateness Method and Delphi voting process. Treatments were recommended as Appropriate, Uncertain, or Not Appropriate, for each of four clinical sub-phenotypes and accompanied by 1–10 risk and benefit scores.

Results: Appropriate treatment modalities for all individuals with knee OA included biomechanical interventions, intra-articular corticosteroids, exercise (land-based and water-based), self-management and education, strength training, and weight management. Treatments appropriate for specific clinical sub-

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phenotypes included acetaminophen (paracetamol), balneotherapy, capsaicin, cane (walking stick), duloxetine, oral non-steroidal anti-inflammatory drugs (NSAIDs; COX-2 selective and non-selective), and topical NSAIDs. Treatments of uncertain appropriateness for specific clinical sub-phenotypes included acupuncture, avocado soybean unsaponfiables, chondroitin, crutches, diacerein, glucosamine, intra-articular hyaluronic acid, opioids (oral and transdermal), rosehip, transcutaneous electrical nerve stimulation, and ultrasound. Treatments voted not appropriate included risedronate and electrotherapy (neuromuscular electrical stimulation).

Conclusion: These evidence-based consensus recommendations provide guidance to patients and practitioners on treatments applicable to all individuals with knee OA, as well as therapies that can be considered according to individualized patient needs and preferences.

Introduction

Osteoarthritis (OA) of the knee is a major cause of pain and locomotor disability worldwide. In January 2010, the OA Research Society International (OARSI) published an update to their evidence-based, consensus recommendations for the treatment of OA of the hip and knee[1]. The 2010 guidelines update followed two previous OARSI guidelines statements[2,3] and included systematic reviews (SRs) of the evidence for relevant therapies and critical appraisals of existing guidelines. Since the publication of the 2010 OARSI guidelines, the evidence base on knee OA treatment has evolved. This guidelines statement aims to incorporate evidence from these recent publications, in addition to the best-available previously published research, to assess where previous treatment recommendations should be modified or expanded to include new OA treatments. Because clinical considerations and availability of evidence between knee OA and hip OA treatments differ, the present guidelines sought to focus specifically on treatment of primary OA of the knee.

For the present guidelines, we endeavored to enhance the applicability of treatment recommendations by stratifying for relevant co-morbidities, and for the presence of OA in joints other than the knee(s). To synthesize the scientific literature and expert opinion, we adopted the RAND/University of California, Los Angeles Appropriateness method[4] and used a modified Delphi method to achieve expert consensus closely integrated with empirical evidence.

This statement updates the previous OARSI recommendations, incorporating literature published between January 2009 and March 2013, to scrutinize the safety and efficacy of new therapies for OA and reexamine existing therapies in light of recent evidence. These recommendations are intended to be used in conjunction with individual patient and physician's values and judgments to optimize OA treatment for different needs. These guidelines are intended for use by practitioners internationally, based on expert views of the relative safety and efficacy of available treatments for OA, irrespective of healthcare reimbursement policies or popular treatment practices.

Methodology

Literature search

Our strategy was to build on the prior OARSI literature review and guidelines by searching for meta-analyses, SRs and randomized controlled trials (RCTs) in the period subsequent to the 2010 guidelines search. The initial literature search was conducted in the first quarter of 2012, and was based on treatments from the OARSI 2010 guidelines in addition to new treatments proposed by the Osteoarthritis Guidelines Development Group (OAGDG). The search was last updated in March 2013.

We deployed electronic searches in Medline, EMBASE, Google Scholar, Web of Science, and the Cochrane Central Register of Controlled Trials using relevant subject headings and keywords and then hand-searched the reference lists of all retrieved studies and abstracts presented at pertinent scientific meetings. Publications eligible for inclusion in our literature summary were (1) the most current SRs and/or meta-analyses and (2) any randomized clinical trials published subsequent to those SRs. If multiple SRs were published in a similar time period, all were included. If no SRs or meta-analyses were available, all published RCTs were included.

Literature summary

Our approach to summation of the evidence was to update the literature summary for the prior recommendations with high-quality evidence that emerged subsequent to its publication in 2010. We selected the best-available evidence to inform guidelines development. Meta-analyses, SRs and RCTs were considered to be the highest level of evidence. The value of meta-analyses for a literature synthesis is that they provide insight across the range of available RCTs on a topic as well as forest plots, sensitivity analyses and pooled results. The data extraction team produced a summary for each intervention that included description of the study methodology with full citations, any reported safety information, and relevant outcomes including effect sizes.

The quality and level of evidence available for each treatment modality was graded according to the following:

Level/type of evidence: The highest level of available evidence used (e.g., SR and/or most current RCT).

Quality of evidence: The methodological rigor of the highest level of evidence used. Meta-analyses and SRs were assigned a quality rating of "Good", "Fair", or "Poor" using the Assessment of Multiple Systematic Reviews Tool (AMSTAR). The Cochrane Risk of Bias Assessment Method was used to rate RCTs.

Estimated Effect Sizes: If the level of evidence listed above included a meta-analysis, the Estimated Effect Size for pain *versus* control was stated from that meta-analysis. Only pooled effect sizes reported as a standardized mean difference (SMD) were reported.

Thus, the expert panel was informed with the prior OARSI guideline publications, subsequent publications generated by the literature search, and a literature summary (Bibliography available as supplement). We provided the literature summary to the OAGDG in August of 2012.

Composition of the expert panel

The OAGDG expert panel was composed of 13 voting members and a patient advocate. This group was selected for its diverse expertise and experience in OA management. The panel included seven rheumatologists (NA, FB, GH, DH, KK, TM, FR), two orthopedic surgeons (HK, SL), two physical therapists (SBZ, ER), one primary care practitioner and clinical guidelines methodologist (MU), and one physical therapy and rehabilitation specialist (YH). These

members have experience in both academic medicine and private practice, and also have expertise in clinical epidemiology and other research methodology (Appendix 1).

Management of conflict of interest (COI)

At the request of the OARSI Ethics Committee, all members of the OAGDG were required to complete a COI questionnaire to report any potential conflicts including consulting, grant support, practice revenue, intellectual property, etc. for each treatment (Appendix 1). During initial rounds of voting, OAGDG members were instructed to recuse themselves from voting on potentially conflicted treatment modalities. At the April 2013 OARSI meeting, OAGDG members updated disclosures and discussed these conflicts in person with an ethics committee member prior to the final round of voting. The Ethics Committee representative made a final determination regarding the level at which a potential conflict would disqualify an OAGDG member from voting on each treatment. Final disclosure and voting recusal results were twice distributed among the OAGDG to verify their accuracy.

Role of funding source

This project was commissioned and funded by OARSI, yet was developed independently by the OARSI Treatment Guidelines Committee. The funding source did not participate in the literature search; determination of study eligibility criteria; voting process; data analysis or interpretation; or manuscript preparation. The manuscript was reviewed and approved by OARSI's Executive Committee prior to release for public comment.

OARSI receives sponsorship from Bioiberica, EMD Serono, Expanscience, Rottapharm/Madaus, Abbvie, Astellas, Bioventus, Boston Imaging Core Lab (BICL), Chondrometrics, Fidia Pharma USA, Flexion, Perceptive Informatics, Merck, Seikagaku, Servier, and Zimmer. No direct medical industry support was used or requested for guideline development. Guidelines development was a budgeted item in OARSI's annual budget.

Formulation of recommendations

Role of the expert panel

The literature summary was released to the OAGDG in August of 2012. An updated literature summary was released in October 2012 to inform subsequent rounds of voting (Bibliography available in supplement). Their role was to use the evidence base along with their expert knowledge, to provide votes on the appropriateness of each treatment modality, according to RAND/UCLA methodology[4], and also an assessment of benefit and risk. The RAND/UCLA methodology is a highly-established approach that was explicitly developed to leverage expert opinion about interventions in situations where the evidence may be incomplete.

After an initial round of voting that occurred after viewing the evidence, but prior to any discussion, the results were scrutinized by the OAGDG using an online forum to generate discussion and clarifications. Subsequent rounds of voting were performed to with further stratifications of treatment modalities (e.g., non-steroidal anti-inflammatory drugs (NSAIDs) were split into non-selective, selective COX-2 inhibitors, and topical) in October of 2012, March of 2013, and during the OAGDG's face-to-face meeting in April of 2013.

OA clinical sub-phenotypes. In order to enhance the specificity of the treatment recommendations for individuals with varying health profiles and OA burden, we defined four clinical sub-phenotypes (Table I). The rationale for these stratifications was that co-morbidities and the presence of OA in other joints might influence treatment choices. However, in all situations the voting was focused on treatment of the knees, and not on treatment of the non-knee joints. The OAGDG also decided on treatments that might merit separate evaluation of symptomatic and structural outcomes.

Voting and scoring. For each treatment modality, the OAGDG voted on appropriateness using a nine-point scale (1–9), therapeutic benefit on a 10-point scale (1–10), and overall risk on a 10-point scale (1–10).

According to the RAND/UCLA Appropriateness Method[4], the panelists ranked the appropriateness of each treatment on a nine-point scale, in which a score in the range 1–3 is considered 'inappropriate', 4–6 'uncertain', and 7–9 'appropriate'. We then pooled these scores to generate a median appropriateness score for each treatment according to patient sub-phenotype. In addition, according to RAND/UCLA methodology, we classified the presence of 'disagreement' among the votes for a treatment modality if greater than one-third fell in the opposite tertile to the median score [e.g., a vote was considered in "Disagreement" if it received an "Appropriate" median vote ($\geq$7) with five of 13 members voting "Not appropriate" ($\leq$3)]. Finally, we classified a treatment as "Appropriate" if it received a median score of $\geq$7 without disagreement. A treatment was classified as "Not appropriate" if it received a median vote of $\leq$3 or lower without disagreement. A treatment receiving a score between 3 and 6, or a treatment with disagreement, was classified as "Uncertain". An "Uncertain" recommendation can reflect either the ambiguous state of current evidence or equivocal appropriateness either due to a moderately unfavorable risk profile or to limited efficacy. However, the 'uncertain' classification is not intended to be a negative recommendation or preclude use of that therapy. Rather it indicates a role for physician–patient interaction in determining whether this treatment may have merit in the context of their individual characteristics, co-morbidities and preferences.

Each OAGDG member also voted separately on the level of risk and the level of benefit associated with each treatment. Risk was

Table I
Stratification into sub-phenotypes

OA joint type	**Knee-only OA**: Symptomatic OA in one or both knees only. **Multiple-joint OA***: Symptomatic OA of the knee(s) in addition to other joints (e.g., hip, hand, spine, etc).
Co-morbidities	**No co-morbidities**: The individual with OA has no pertinent co-morbid health concerns. **Co-morbidities**: The individual with OA has any of the following pertinent co-morbid health concerns: diabetes; hypertension; CV disease; renal failure; gastrointestinal (GI) bleeding; depression; or physical impairment limiting activity, including obesity. • **Moderate co-morbidity risk**†: The individual with OA has any of the following pertinent co-morbid health concerns: diabetes; advanced age; hypertension; CV disease; renal failure; GI complications; depression; or physical impairment limiting activity, including obesity. • **High co-morbidity risk**†: The individual with OA has risk factors such as history of GI bleed, myocardial infarction, chronic renal failure, etc.

* Defines a clinical sub-phenotype. Recommendations refer to treatment of the knee(s) in such individuals.

† For Oral NSAIDs (both non-selective and selective COX-2 inhibitors). Further stratification of risk categories was considered necessary for these treatments given the important safety implications and substantial availability of safety data.

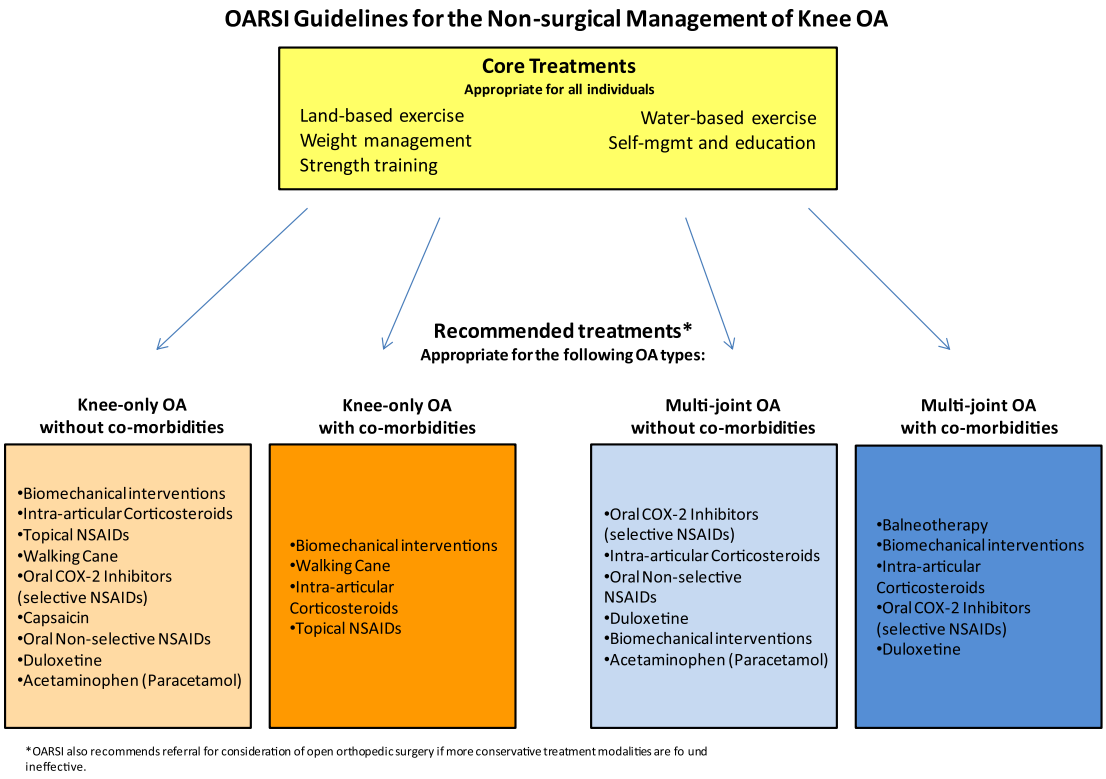


Fig. 1. Appropriate treatments summary.

scored from 1 (least risk) to 10 (most risk) and benefit was scored from 1 (no benefit) to 10 (most beneficial). The group's mean risk and benefit scores [along with 95% confidence intervals (CIs)] for each treatment are plotted separately as bar graphs within the guidelines statement (Appendix 2: Annotated Figure).

The OARSI guidelines report was drafted after a face-to-face meeting and re-vote at the OAGDG meeting at the April 2013 OARSI World Congress. These guidelines provide recommendations according to the median "appropriateness" scores voted upon by a panel of expert physicians and researchers based on their knowledge and the literature summary.

Figure 1 provides a summary of all treatments voted "Appropriate," organized by clinical sub-phenotype. The OAGDG's median voting scores for appropriateness, upon which the recommendations are based, are appended in a summary table (Appendix 3). Also included are the OAGDG's mean risk scores, benefit scores, and composite benefit and risk scores for each treatment and clinical sub-phenotype. The composite benefit and risk score is the product of the benefit score (1–10) and the transposed risk score (where 1 = highest and 10 = safety) yielding a range of 1 (worst) to 100 (best).

Public comment. The guidelines report draft was disseminated for public comment between September 4th and 18th, 2013. At the conclusion of the public comment period, public responses to the guidelines report were distributed among the OAGDG in order to formulate an appropriate response. Consistent with the OAGDG's prior procedures, it was determined that omission of any research within the committee's original literature summary criteria would necessitate a re-vote on the treatment for which evidence was omitted. Additional evidence for balneotherapy and chondroitin was brought to the attention of the OAGDG during public comment, resulting in an update of the evidence report and a re-vote on each of these interventions by the OAGDG expert panel. To incorporate the new chondroitin evidence, pooled analyses of pain and function outcomes were conducted for randomized clinical trials of chondroitin in knee OA. The balneotherapy evidence was considered too heterogeneous to permit pooled analysis. The finalized guidelines report draft was submitted for publication following approval of the OARSI Executive Committee.

Recommendations

Non-pharmacological interventions

Acupuncture

Recommendation:

- **Uncertain**

Rationale:

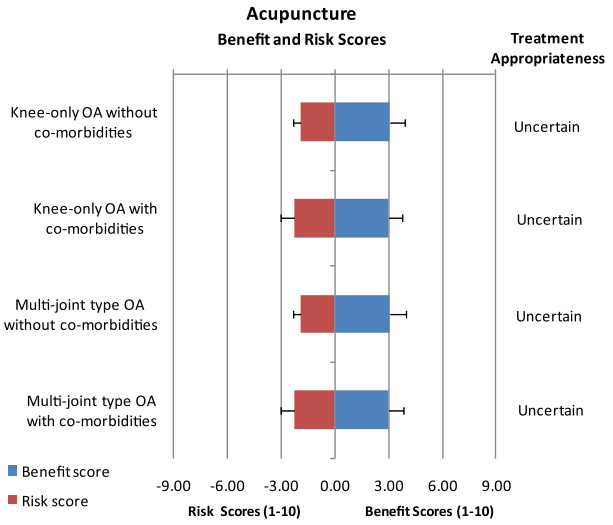
The efficacy of acupuncture for peripheral joint OA has been tested in numerous clinical trials. Trials using waiting list- or usual care control groups, have generally found a clinically relevant benefit, but those using a sham-acupuncture have been less positive[5]. A recent pooled analysis of 16 RCTs found statistically significant benefit of acupuncture in sham-controlled trials, though this did not reach the investigators' threshold for clinical significance[5].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for

Pain (SMD): 0.28 (0.11–0.45)[5].
Function (SMD): 0.28 (0.09–0.46)[5].



Balneotherapy/spa therapy

Recommendation:

- **Appropriate**: individuals with multiple-joint OA and relevant co-morbidities
- **Uncertain**: individuals without relevant co-morbidities
- **Uncertain**: individuals with knee-only OA

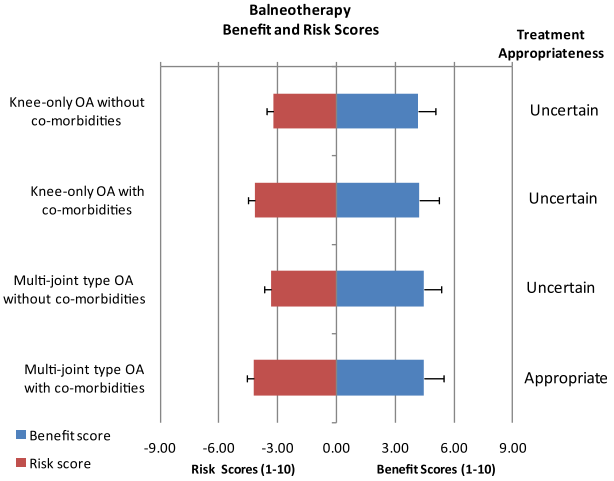
Rationale:

Balneotherapy (defined as the use of baths containing thermal mineral waters) includes practices such as Dead Sea salt or mineral baths, sulfur baths, and radon-carbon dioxide baths. Two 2009 SRs and a 2009 RCT demonstrated benefit of balneotherapy for pain when compared with controls, but the methodologic quality of trials was poor and both reviews concluded that additional large and well-designed RCTs are needed[6–8]. No significant safety concerns were found to be associated with balneotherapy, though reporting of adverse events was patchy among included trials[7,9]. In the voting, balneotherapy was considered appropriate only for the sub-phenotype with multiple-joint OA and co-morbidities, due to paucity of treatment alternatives for that group.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Fair.

Estimated Effect Size for Pain or Function: Not available.



Biomechanical interventions

Recommendation:

- **Appropriate**

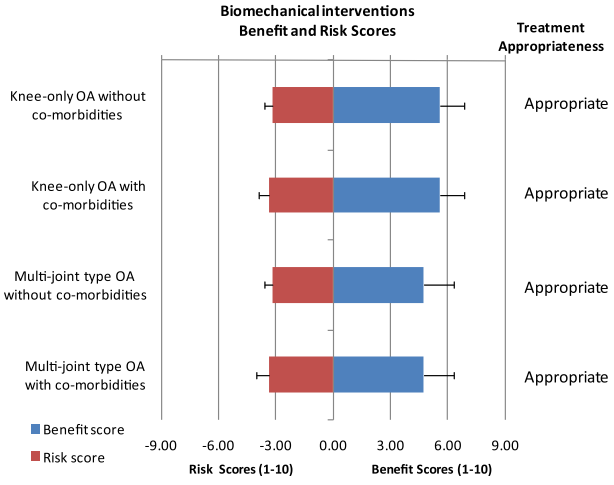
Rationale:

We recommend use of biomechanical interventions as directed by an appropriate specialist. A 2011 SR and three recent RCTs evaluated the effectiveness of knee braces, knee sleeves, and foot orthoses in conservative management of knee OA[10–13]. One review suggested that knee braces and foot orthoses were effective in decreasing pain, joint stiffness, and drug dosage and also improved physical function, with insignificant adverse events[10]. The conclusions were limited due to the heterogeneity and poor quality of available evidence. Results regarding lateral wedge insoles varied, with one RCT demonstrating no symptomatic or structural benefits[11] and another asserting their appropriateness as a possible alternative to valgus bracing for conservative medial knee OA treatment[12]. One recent RCT found that variable-stiffness walking shoes reduced adduction movement and pain and improved function after 6 months of wear, though this benefit was not statistically significant when compared to constant-stiffness footwear[13].

Quality assessment:

Level of evidence: SR of RCTs and non-randomized clinical trials.
Quality of evidence: Fair.

Estimated Effect Size for Pain or Function: Not available.



Cane (walking stick)

Recommendation:

- **Appropriate**: knee-only OA
- **Uncertain**: multiple-joint OA

Rationale:

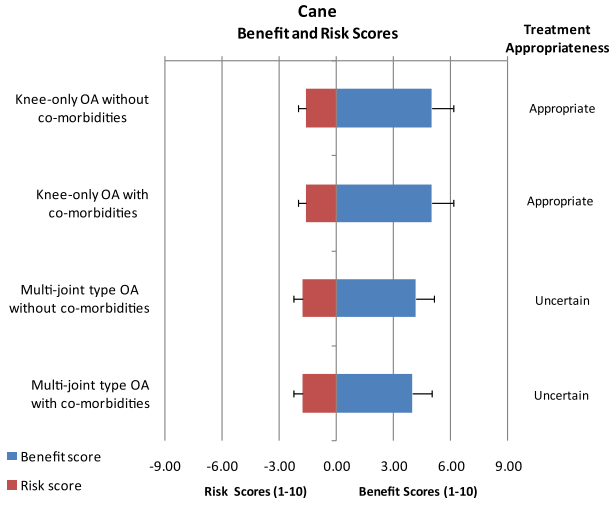
A single-blind RCT concluded that canes, in comparison with usual disease management, could be used to diminish pain and improve function and some aspects of quality of life in participants with knee OA[14]. A substantial increase in energy expenditure in the first month of cane use was no longer a factor for concern by the end of the second month. There was a lack of evidence regarding

cane use for individuals with multiple-joint type OA. This treatment could be inappropriate for some such individuals, as cane use to relieve knee pain may increase weight-bearing load on other affected joints (e.g., contralateral hand and hip joints), though further research is needed to confirm this.

Quality assessment:

Level of overall evidence: Single-blind RCT.
Quality of overall evidence: Fair.

Estimated Effect Size for Pain or Function: Not available.



Crutches

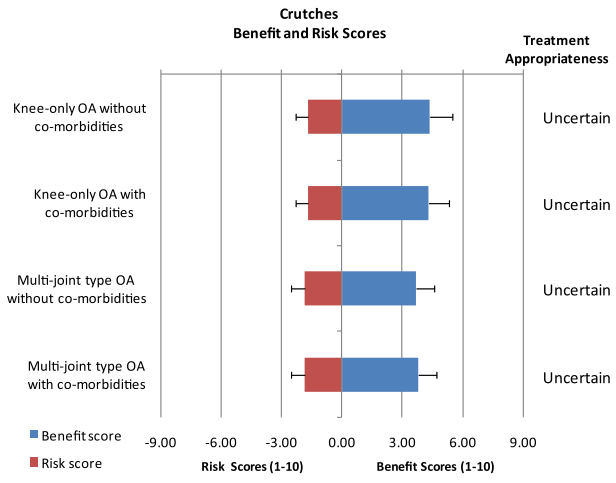
Recommendation:

- **Uncertain**

Rationale:

There is insufficient evidence at this time to support the use of crutches as an appropriate alternative to cane use.

Level of Evidence: Expert consensus of OAGDG.
Quality of evidence: No available trials.
Estimated Effect Size for Pain or Function: Not available.



Electrotherapy/neuromuscular electrical stimulation

Recommendation:

- **Not appropriate**

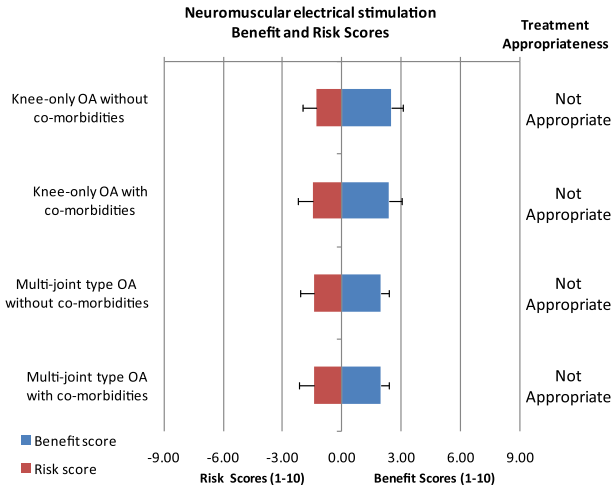
Rationale:

A 2012 SR and meta-analysis demonstrated conflicting efficacy data for neuromuscular electrical stimulation and concluded that additional studies were needed to determine the efficacy of this intervention[15]. A recent RCT showed no significant additive effect of electromyograph (EMG) biofeedback to strengthening exercise for pain, function and muscle strength in 40 participants with knee OA[16].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Fair.

Estimated Effect Size for Pain or Function: Not available.



Exercise (land-based)

Recommendation:

- **Appropriate**

Rationale:

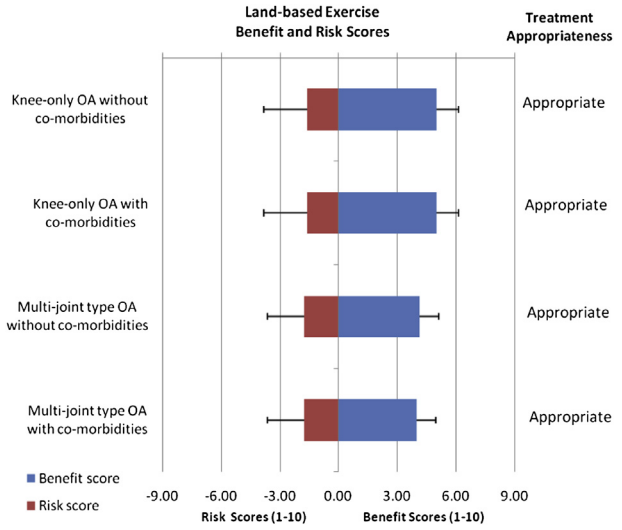
Four recent meta-analyses found small but clinically relevant short-term benefits of land-based exercise for pain and physical function in knee OA[17–20]. Meta-analyses investigating t'ai chi found strong favorable benefits of t'ai chi for improving pain and physical function in individuals with knee OA[21,22]. The duration and type of exercise programs included in these meta-analyses varied widely, but interventions included a combination of elements including strength training, active range of motion exercise, and aerobic activity. Results were generally positive among land-based exercise type, and did not significantly favor any specific exercise regimens[17–20].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for

Pain (SMD): Ranges from 0.34 (0.19–0.49)[17] to 0.63 (0.39–0.87)[21].
Function (SMD): 0.25 (0.03–0.48)[17].



Exercise (water-based)

Recommendation:

- **Appropriate**

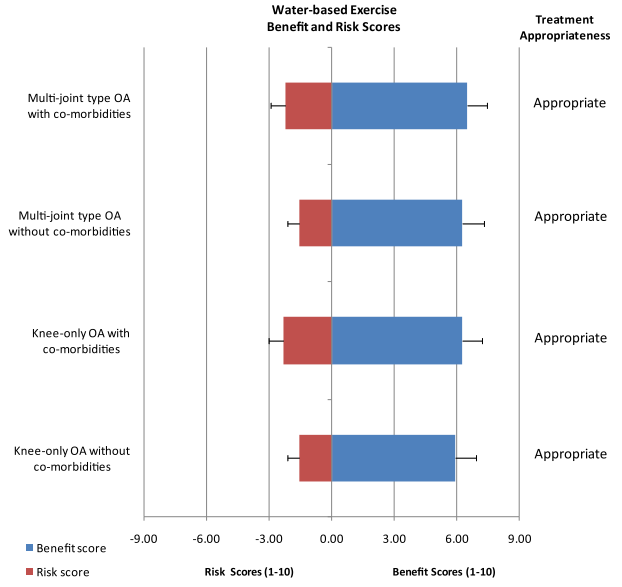
Rationale:

A 2007 SR investigating water-based exercise in knee and hip OA found small to moderate short-term benefits for function and quality of life, but only minor benefits for pain[23].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs and quasi-randomized trials.
Quality of evidence: Good.

Estimated Effect Size for Pain or Function: Not available.



Strength training

Recommendation:

- **Appropriate**

Rationale:

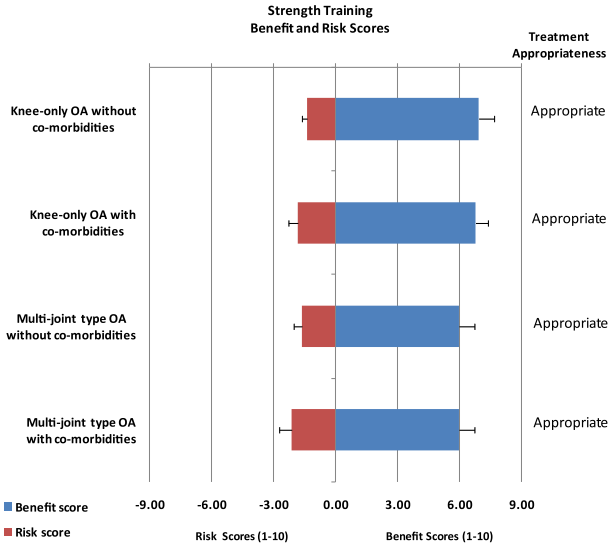
A 2011 meta-analysis and SR demonstrated moderate effect sizes of strength training for reducing pain and improving physical function compared with controls[17]. Strength training programs primarily incorporate resistance-based lower limb and quadriceps strengthening exercises. Both weight-bearing and non-weight-bearing interventions were included, as well as group and individual programs. Participants experienced similarly significant improvement with each of these programs.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for

Pain (SMD): 0.38 (0.23–0.54)[17].
Function (SMD): 0.41 (0.17–0.66)[17].



Self-management and education

Recommendation:

- **Appropriate**

Rationale:

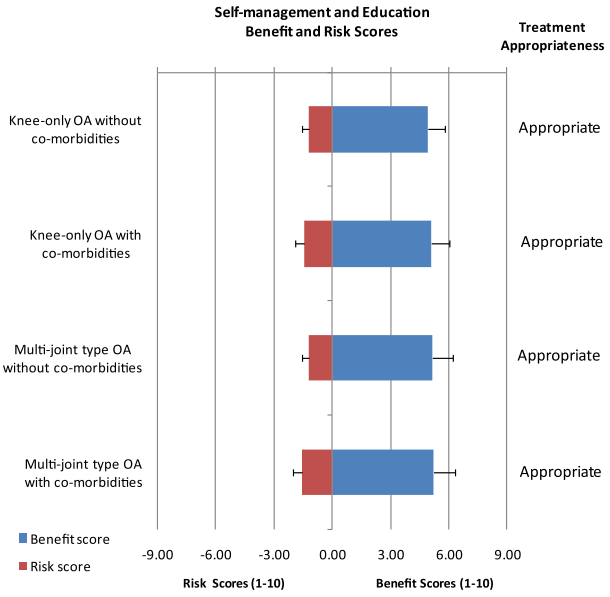
A 2011 meta-analysis and a 2005 meta-analysis found moderate benefits of self-management programs for chronic musculoskeletal pain conditions on measures of pain and disability[24,25]. Analysis of arthritis-related disability showed only modest benefit. Recent randomized clinical trials indicated significant clinical benefits of self-management[26,27] and suggested feasibility of implementation in primary care by means of group sessions[28] and telephone-based sessions[29]. Another RCT expressed reservations about the efficacy and practicality of such interventions[30].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Sizes for

Pain (SMD): Ranges from 0.06 (0.02–0.10)[25] to 0.29 (0.17–0.41)[24].



Transcutaneous electrical nerve stimulation (TENS)

Recommendation:

- **Uncertain**: knee-only OA
- **Not appropriate**: multiple-joint OA

Rationale:

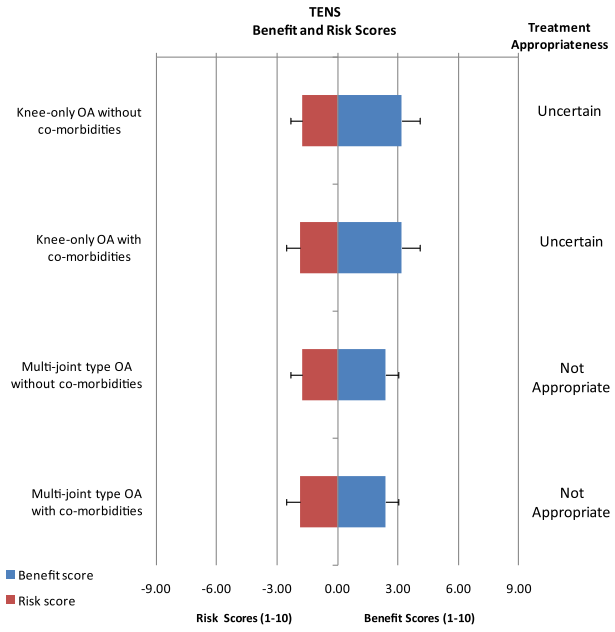
A 2009 SR found inconclusive results regarding the effect of TENS for pain relief in knee OA[31]. Due to the low methodological quality and high heterogeneity of included trials, no effect size was reported as a primary result. The review found no evidence to suggest that TENS was unsafe. A recent RCT revealed no statistically significant difference for pain between TENS and a sham TENS procedure[32].

Quality assessment:

Level of evidence: SR of randomized or quasi-randomized clinical trials.
Quality of evidence: Good.

Estimated Effect Size for

Pain (SMD): 0.07 (−0.32–0.46)[31].
Function (SMD): 0.34 (0.14–0.54)[31].



Weight management

Recommendation:

- **Appropriate**

Rationale:

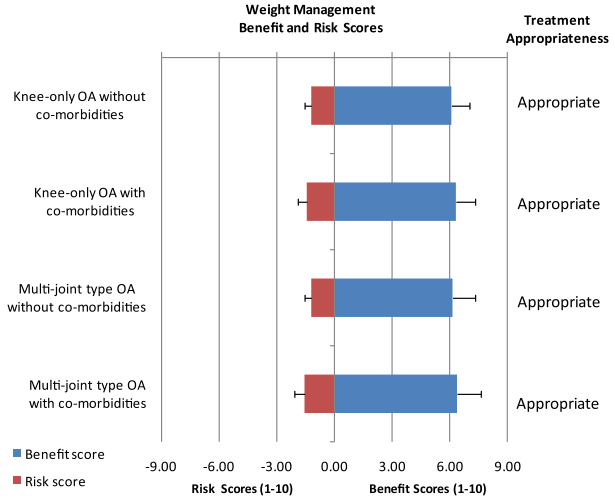
A 2007 SR and meta-analysis found reductions in pain and physical disability for overweight participants with knee OA after a moderate weight reduction regime[33]. The analysis supported the notion that a weight loss of 5% should be achieved within a 20-week period—that is, 0.25% per week—for the treatment to be efficacious.

Quality assessment:

Level of overall evidence: SR and meta-analysis of RCTs.
Quality of overall evidence: Good.

Estimated Effect Size for

Pain (SMD): 0.20 (0.0–0.39)[33].
Function (SMD): 0.23 (0.04–0.42)[33].



Ultrasound

Recommendation:

- **Uncertain**: knee-only OA
- **Not appropriate**: multiple-joint OA

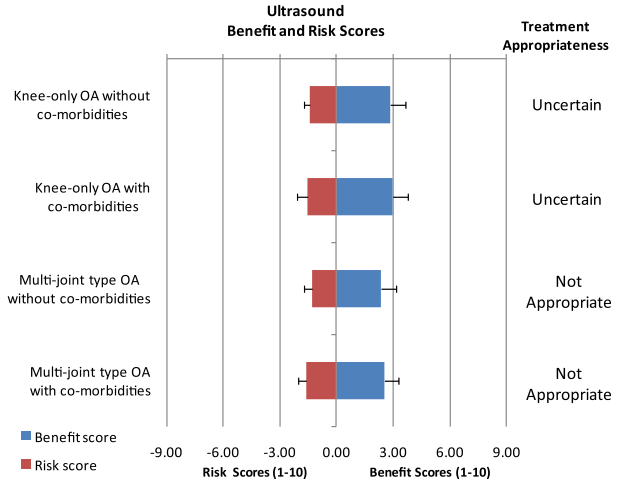
Rationale:

Two 2010 SRs suggested a possible beneficial effect of ultrasound for knee OA; however, the quality of the analyzed evidence was low[34,35]. No safety risks were reported to be associated with ultrasound. A 2012 RCT found no significant differences between the groups for pain or function[36].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain (SMD): Ranges from 0.49 (0.18–0.79)[35] to 0.49 (0.23–0.76)[34].



Pharmacological interventions

Acetaminophen (paracetamol)

Recommendation:

- **Appropriate**: individuals without relevant co-morbidities
- **Uncertain**: individuals with relevant co-morbidities

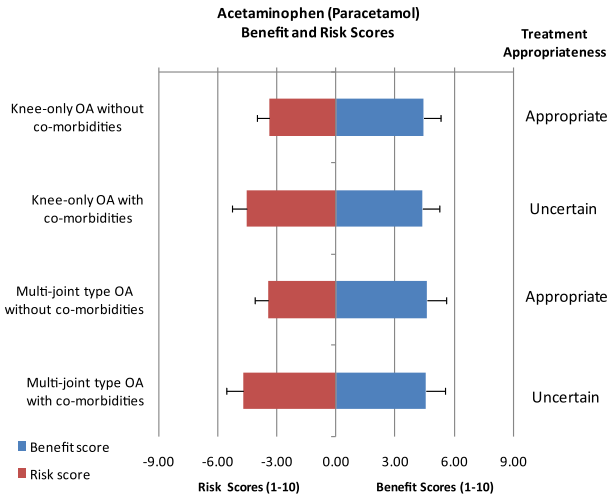
Rationale:

A 2010 SR and meta-analysis abstract found a low-level effect of acetaminophen for OA pain, suggesting usefulness as a short-term analgesic[37]. However, both this review and a 2012 safety review indicated increased risk of adverse events associated with acetaminophen use, including GI adverse events and multi-organ failure[38]. These recent findings suggest greater risk associated with acetaminophen use (particularly when used for extended durations) than previously thought. Thus, we recommend conservative dosing and treatment duration consistent with approved prescribing limits.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain (SMD): 0.18 (0.11–0.25)[37].



Avocado soybean unsaponfiables (ASU)

Recommendation:

- **Uncertain**

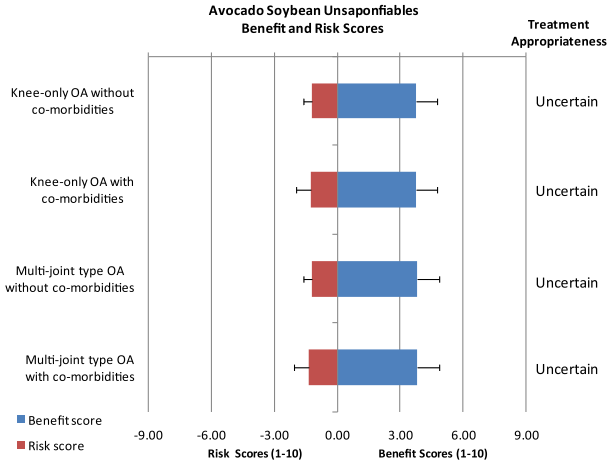
Rationale:

A 2008 SR and meta-analysis comparing ASU with oral placebo in 644 patients with knee and hip OA demonstrated a small benefit for pain in favor of ASU that was more evident in knee OA[39].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain (SMD): 0.39 (0.01–0.76)[39].



Capsaicin

Recommendation:

- **Appropriate**: knee-only OA without relevant co-morbidities
- **Uncertain**: multi-joint OA and individuals with relevant co-morbidities

Rationale:

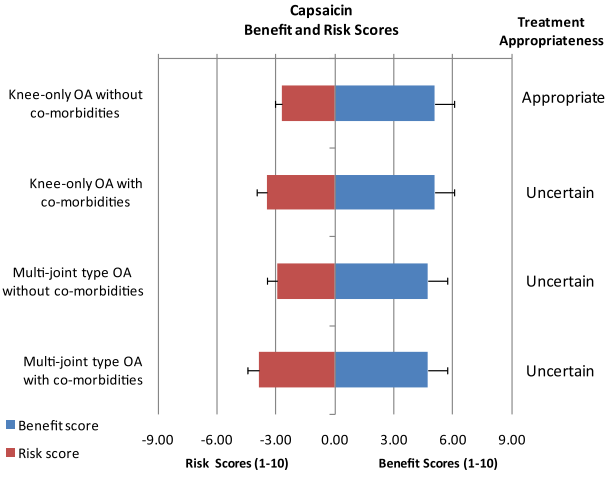
Citing a previous SR[40] and RCT[41], a 2011 comparative efficacy review concluded that topical capsaicin was superior to placebo for

50% pain reduction (number needed to treat 8.1) but associated with increased local adverse events [54% vs 15%; relative risk (RR) 3.6 (95% CI: 2.6–5.0)] and withdrawals due to adverse events [13% vs 3%; RR 4.0 (95% CI: 2.3–6.8)][42].

Quality assessment:

Level of evidence: SR of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain and Physical function: Not available.



Corticosteroids (intra-articular injection)

Recommendation:

- **Appropriate**

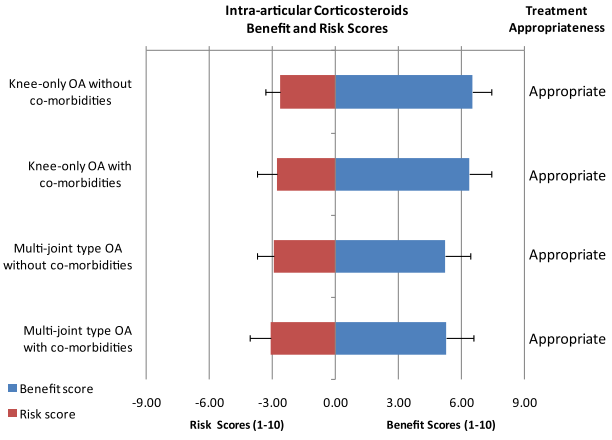
Rationale:

Two recent SRs demonstrated clinically significant short-term decreases in pain[43,44]. Short-term effects were found to be significantly greater than those of intra-articular hyaluronic acid. The reviews concluded that for longer duration of pain relief, clinicians should consider other treatment options.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain: Not available.



Chondroitin (for symptom relief)

Recommendation:

- **Uncertain**

Chondroitin (for disease modification)

Recommendation:

- **Not appropriate**

Rationale:

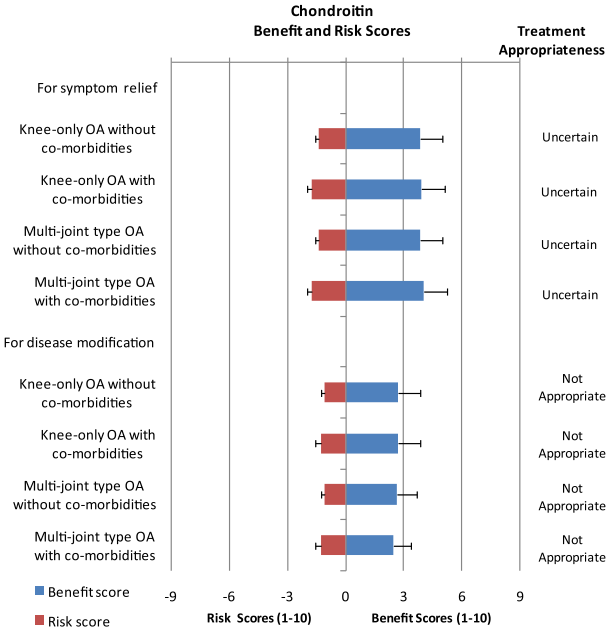
Four SRs examined the efficacy of chondroitin for knee OA[45–48]. Results differed regarding symptom relief, with some reviews finding no significant benefit of chondroitin over placebo for pain and others finding large effect sizes in favor of chondroitin. A high degree of heterogeneity and small, poor quality included trials in one meta-analysis made definitive assessment difficult[46]. Effect sizes for pain were small to non-existent [e.g., 0.01 (95% CI: −0.07–0.13)] in stratified analyses of large-scale, high-quality trials[46]. Another meta-analysis showed no statistically significant benefit of chondroitin when compared with placebo[45]. Results were also mixed regarding disease modification, with only some studies showing statistically significant decreases in joint-space narrowing (JSN) over longer (2-year) follow-up[47,48].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain (SMD): Ranges from 0.13 (0.00–0.27)[45] to 0.75 (0.50–0.99)[46].

Estimated Effect Size for reduction in rate of decline of minimum joint-space width (SMD): Ranges from 0.26 (0.14–0.38)[47] to 0.30 (0.00–0.59)[48].



Diacerein

Recommendation:

- **Uncertain**

Rationale:

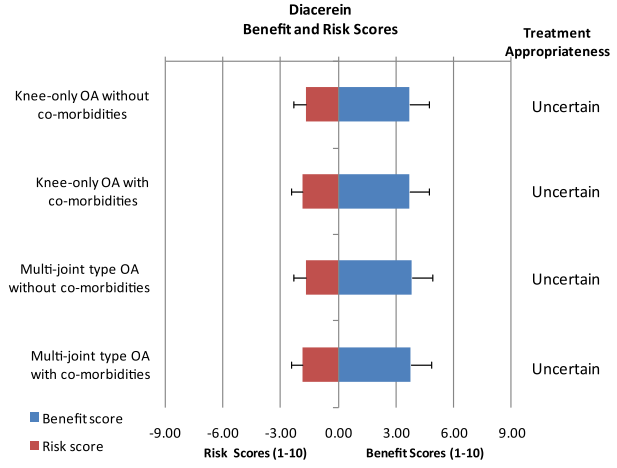
A 2010 SR and meta-analysis found a small but statistically significant short-term benefit of diacerein for pain compared with placebo, despite a large degree of heterogeneity among included trials[49]. The review also found a significantly increased risk of diarrhea among those receiving diacerein [RR = 3.51 (95% CI: 2.55–4.83, $P < 0.001$)]. The study authors suggested that diacerein may still be a safer alternative to NSAIDs, which are associated with more severe adverse events, but also concluded that more high-quality trials are needed to confirm the efficacy of diacerein and rule out publication bias.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for

Pain (SMD): 0.24 (0.08–0.39)[49].
Function (SMD): 0.14 (0.03–0.25)[49].



Duloxetine

Recommendation:

- **Appropriate**: individuals without co-morbidities
- **Appropriate**: individuals with multiple-joint OA and relevant co-morbidities
- **Uncertain**: knee-only OA with relevant co-morbidities

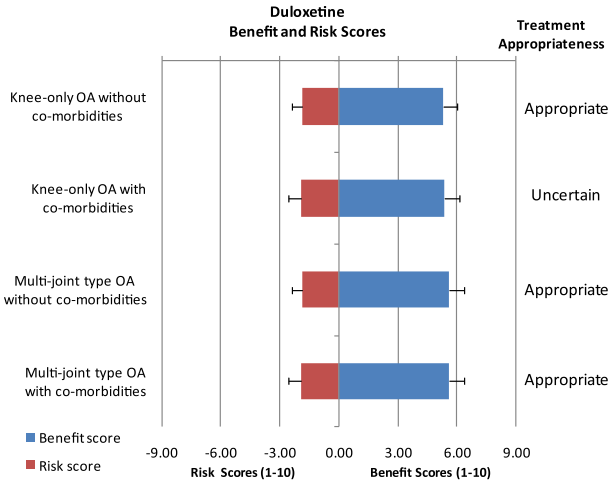
Rationale:

A 2012 SR and a 2011 RCT comparing duloxetine with oral placebo found duloxetine efficacious and tolerable for chronic pain associated with OA[50,51]. Pooled analysis found that 16.3% of the patients who received duloxetine withdrew due to adverse events compared with 5.6% of those receiving placebo[50]. The most commonly reported adverse events included nausea, dry mouth, somnolence, fatigue, constipation, decreased appetite, and hyperhidrosis. While duloxetine was considered appropriate for most clinical sub-phenotypes, associated adverse events and availability of more targeted therapies predicated uncertain appropriateness for individuals with knee-only OA and co-morbidities.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Fair.

Estimated Effect Size for Pain: Not available.



Glucosamine (for symptom relief)

Recommendation:

- **Uncertain**

Glucosamine (for disease modification)

Recommendation:

- **Not appropriate**

Rationale:

Two SRs comparing glucosamine with placebo for OA found mixed results regarding the efficacy of glucosamine for pain relief and physical function[45,52]. One review found no statistically significant benefit of glucosamine for pain[45] and the other found a positive effect for pain that did not reach statistical significance when confined to studies with adequate allocation concealment[52]. The most recent meta-analysis[45] included a large, NIH-funded RCT (GAIT study) that had a null result for glucosamine for pain relief[53]. Regarding disease modification, a SR found no statistically significant differences in minimum JSN between glucosamine and placebo at 1-year follow-up, though a moderate effect was detected at 3 years[48]. A 2011 safety review found that long-term use of glucosamine was not associated with cardiovascular (CV) safety risks[54]. Two more meta-analyses found no increase in overall adverse events relative to placebo[45,52]. Small pooled effect sizes (especially for the large high-quality studies), inconsistency in results between industry-sponsored and independent trials, and heterogeneity among studies generated uncertainty as to the appropriateness of glucosamine.

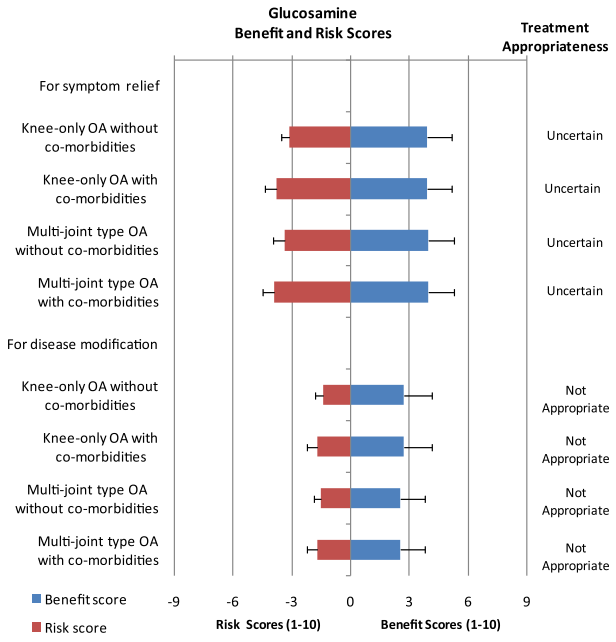
Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.

Quality of evidence: Good.

Estimated Effect Size for Pain (SMD): Ranges from 0.17 (0.05, 0.28)[45] to 0.47 (0.23–0.72)[52].

Estimated Effect Size for reduction in rate of decline of minimum joint-space width (SMD): 0.08 (−0.12–0.27)[48].



Hyaluronic acid (intra-articular injection)

Recommendation:

- **Uncertain**: knee-only OA
- **Not appropriate**: multiple-joint OA

Rationale:

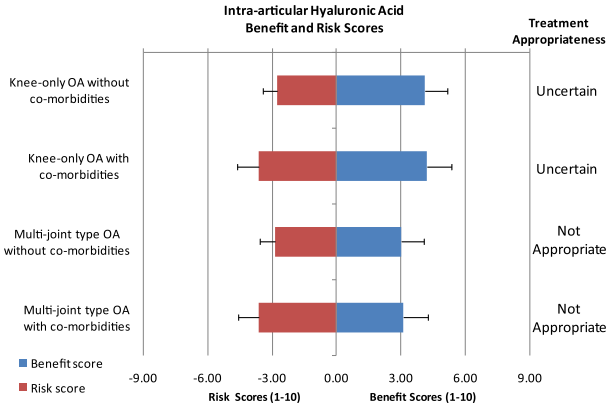
A recent SR demonstrated small but significant efficacy of intra-articular hyaluronic acid for knee OA pain by week 4 with a peak at week 8 (reaching moderate clinical significance) and residual benefit until 24 weeks[55]. Another review found moderate benefits of IAHA for pain and physical function in knee OA, though sensitivity analyses including larger trials or trials with adequate blinding found only small effect size for pain[56]. A third review comparing IAHA with intra-articular corticosteroids (IACS) found that while IACS provided greater benefit for pain 2 weeks after injection, IAHA provided greater benefit at 12 and 26 weeks[43]. Inconsistent conclusions among the meta-analyses and conflicting results regarding IAHA's safety influenced panel votes.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for

Pain (SMD): Ranges from 0.37 (0.28–0.46)[56] to 0.46 (0.28–0.65)[55].
Physical function: 0.33 (0.22–0.43)[56] to 0.31 (0.11–0.51)[55].



NSAIDs (oral non-selective NSAIDs)

Recommendation:

- **Appropriate**: individuals without co-morbidities
- **Uncertain**: individuals with moderate co-morbidity risk
- **Not appropriate**: individuals with high co-morbidity risk

Gastroprotection:

- We do not recommend proton-pump inhibitor (PPI) co-prescription with non-selective oral NSAIDs for those with no co-morbidity risk. For those with moderate or high co-morbidity risk receiving oral non-selective NSAIDs, we recommend PPI co-prescription, though we strongly advise against using oral NSAIDs altogether for individuals with high co-morbidity risk.

Rationale:

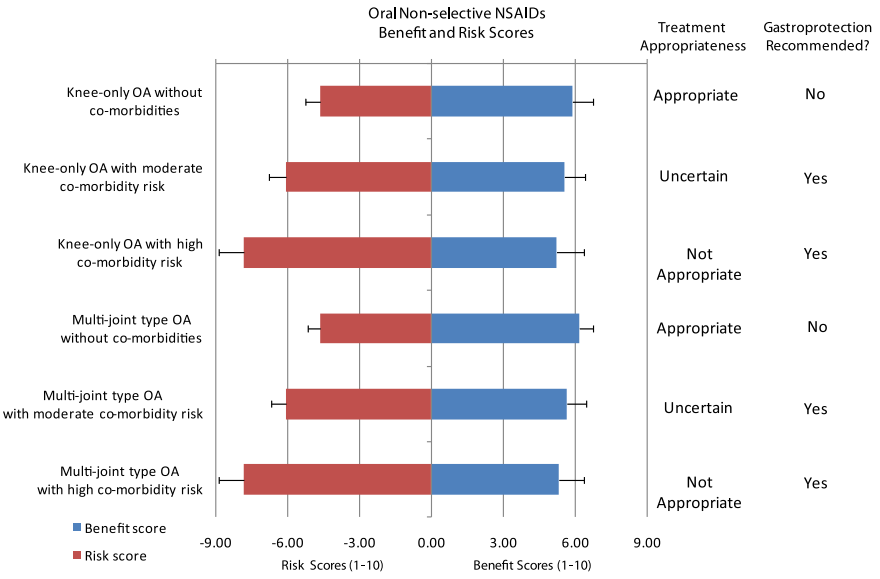
A 2011 comparative effectiveness review indicated that NSAIDs are associated with increased risk of serious GI, CV, and renal harms compared with placebo[42]. Nevertheless, the CV safety of naproxen appeared moderately superior to that of any COX-2 selective NSAID in two SRs of RCTs. Among currently marketed NSAIDs, diclofenac is associated with the highest rate of hepatic laboratory abnormalities. Due to serious safety risks associated with oral NSAID use, we recommend conservative dosing and treatment duration consistent with approved prescribing limits.

The 2011 Cochrane review found that co-prescribing of PPIs, misoprostol, and H2-antagonists reduced the risk of endoscopically detected gastroduodenal ulcers compared with placebo in persons prescribed non-selective NSAIDs[42].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain (SMD): 0.37 (0.26–0.49)[57].



NSAIDs (oral COX-2 inhibitors)

- **Appropriate**: individuals without co-morbidities
- **Appropriate**: multiple-joint OA with moderate co-morbidity risk
- **Uncertain**: knee-only OA with moderate co-morbidity risk
- **Not appropriate**: individuals with high co-morbidity risk

Gastroprotection:

- We do not recommend PPI co-prescription with COX-2 selective oral NSAIDs for those with no co-morbidity risk. For individuals with moderate co-morbidity risk, we advocate neither for nor against PPI co-prescription. For individuals with high co-morbidity risk receiving oral COX-2 selective NSAIDs, we recommend PPI co-prescription, though we strongly advise against using oral NSAIDs altogether for such individuals.

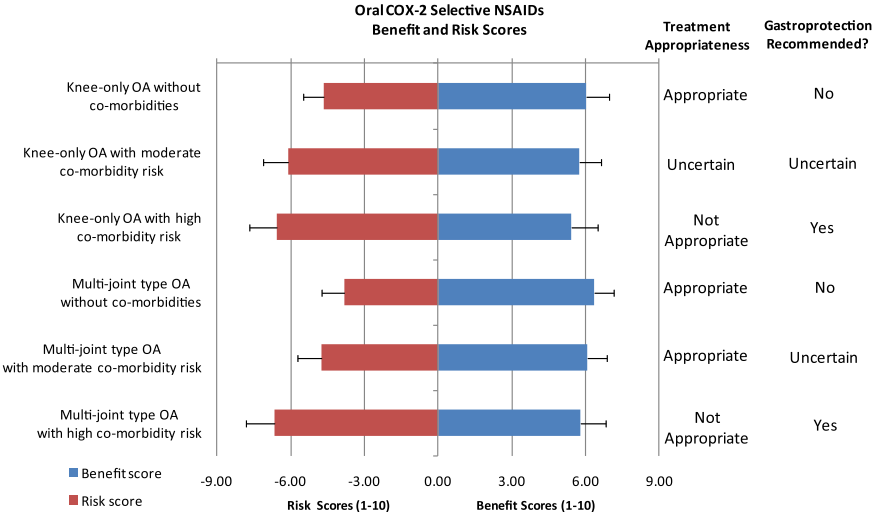
Rationale:

A 2011 comparative effectiveness review found that relative to non-COX-2 selective NSAIDs, selective COX-2 inhibitors were better or comparably tolerated, though rates of serious adverse events were similar[42]. Celecoxib was associated with a lower risk of ulcer complications (RR 0.23, 95% CI: 0.07–0.76) compared with non-selective NSAIDs but a moderately higher risk of CV complications. Due to serious safety risks associated with oral NSAID use, we recommend conservative dosing and treatment duration consistent with US approved prescribing limits.

Quality assessment based on Chou *et al.*[42] and Lee *et al.*[57]:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain: 0.44 (0.33–0.55)[57].



NSAIDs (topical)

Recommendation:

- **Appropriate**: individuals with knee-only OA
- **Uncertain**: individuals with multiple-joint OA

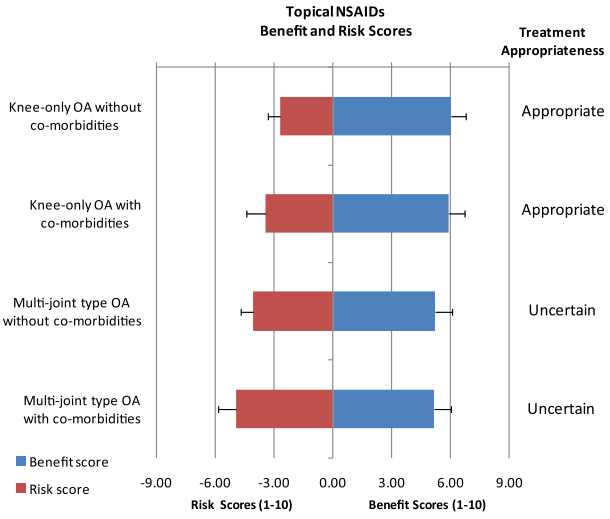
Rationale:

A 2011 Cochrane comparative effectiveness review found comparable efficacy of topical and oral NSAIDs for knee OA[42]. Topical NSAIDs were associated with lower risk of GI adverse events but higher risk of dermatological adverse events compared with oral NSAIDs. Overall, topical NSAIDs were considered to be safer and better tolerated compared with oral NSAIDs.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain: Not available.



Opioids (transdermal)

Recommendation:

- **Uncertain**

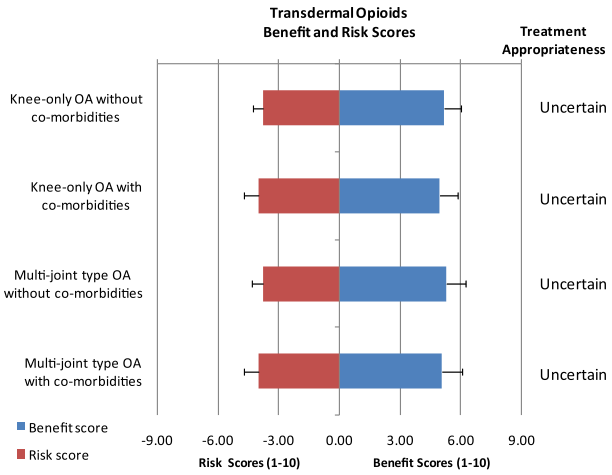
Rationale:

A 2009 SR and meta-analysis examining the efficacy of opioids for knee and hip OA found small effect sizes for pain and physical function for transdermal fentanyl[58]. Patients receiving some form of opioid therapy were four times as likely as patients receiving placebo to withdraw due to adverse events (RR 4.05, 95% CI: 3.06–5.38) and more than three times as likely to experience a serious adverse event (RR 3.35, 95% CI: 0.83–13.56). Thus, the study concluded that opioids offered limited usefulness in the long term.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain (SMD): Ranges from 0.22 (0.03–0.42) to 0.36 (0.26–0.47)[58].



Opioids (oral)

Recommendation:

- **Uncertain**

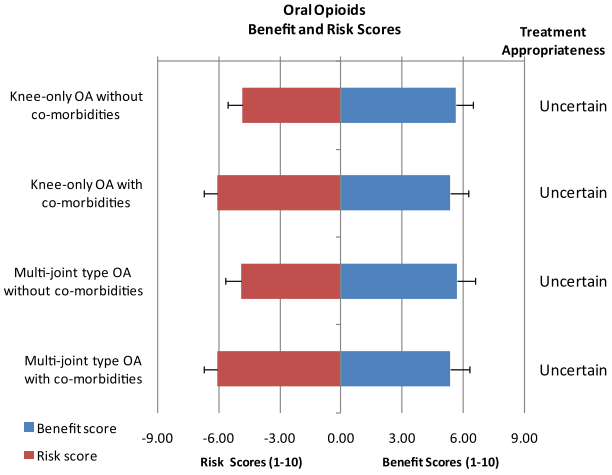
Rationale:

Analyses of pain relief from a 2009 SR found a moderate effect size for codeine over placebo, a small to moderate benefit for oxycodone, and a small benefit for morphine in patients with OA of the knee or hip[58]. A 2006 review also found a small but statistically significant benefit for tramadol over placebo[59]. However, patients receiving some form of opioid therapy were four times as likely as patients receiving placebo to withdraw due to adverse events (RR 4.05, 95% CI: 3.06–5.38) and more than three times as likely to experience a serious adverse event (RR 3.35, 95% CI: 0.83–13.56)[58].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain: Ranges from 0.36 (0.26–0.47) to 0.51 (0.01–1.01)[58].



Risedronate

Recommendation:

- **Not appropriate**

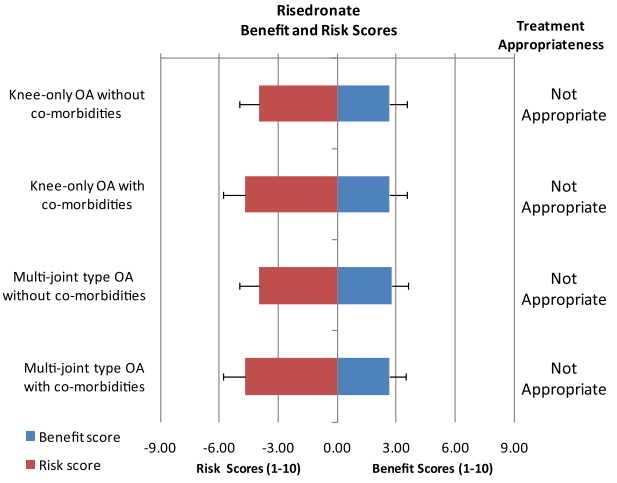
Rationale:

Risedronate was evaluated primarily on its disease-modifying efficacy, as the majority of available evidence targets this outcome. A 2012 SR found that higher doses of risedronate (15 mg/d) did not reduce the signs or symptoms of OA, but did reduce the marker of cartilage degradation (CTX-II), which may contribute to attenuation of radiological progression of OA[60]. The review concluded that further RCTs would be needed to assess the efficacy of risedronate for symptoms, function, and progression of knee OA.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Poor.

Estimated Effect Size for Pain: Not available.



Rosehip

Recommendation:

- **Uncertain**

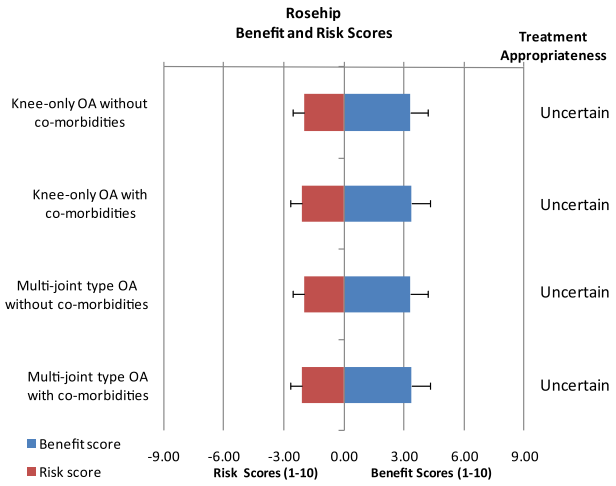
Rationale:

A 2008 SR and meta-analysis of three small trials found a positive effect of rosehip powder for pain when compared with placebo, but the reviewers concluded that further evaluation in larger-scale trials is necessary due to the paucity of available data[61]. Safety results from one included study did not provide conclusive results.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain: 0.37 (0.13–0.60)[61].



Discussion

These OARSI 2013 guidelines for the management of knee OA represent an update to the previous OARSI publications in 2010 and 2008[1,2] and used the original evidence and set of evaluated treatments as the base for a literature update. Their purpose is to disseminate a framework for treatment of knee OA to professionals involved in the management of this disorder, as well as patients, provider organizations and regulatory bodies. The guidelines were also developed for an International context, reflecting the constituency and perspective of OARSI, the sponsoring organization. These guidelines should be used in conjunction with individual patients' values and clinical judgment.

We used the RAND/UCLA approach as a methodology for measuring expert opinion and reaching a classification for appropriateness of each treatment modality[4]. This well-established approach leverages expert opinion in relation to their synthesis of contemporary evidence. One advantage for the field of OA treatment is that it was explicitly developed to measure expert opinion in situations where the evidence may be incomplete. The outcome of the voting process, according to this methodology, is a designation for each putative therapy of "Appropriate," "Uncertain" or "Inappropriate." Among these, the implication of the term "Uncertain" was viewed as unclear by reviewers. To clarify, the "Uncertain" classification is not intended here to be a negative recommendation or to preclude use of that therapy. Rather it requires a role for physician–patient interaction in determining whether this treatment may have merit in the context of its risk-benefit profile and the individual characteristics, co-morbidities and preferences of the patient.

Our guidelines diverge from the previous OARSI guidelines in 2010 and 2008 as well as from recent American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) guidelines by focusing specifically on treatment of OA of the knee. The decision was made to examine knee OA separately due to disparities in available evidence between hip OA and knee OA and differences in best treatment practices between these conditions. The current guidelines aim to identify the best-available treatment practices for knee OA, irrespective of differing healthcare policies and treatment standards internationally. Thus, this update of the OARSI guidelines also excluded cost effective analysis, evaluating treatments solely based upon their safety and efficacy profiles.

Our guidelines also provide separate recommendations for each of four clinical sub-phenotypes. These were assessed separately in order to best capture heterogeneous health profiles and OA disease types. One limitation of this method is that the research literature was not surveyed for OA sites beyond the knee and hip. Thus, recommendations for individuals with multiple-joint OA may not take into account all evidence regarding other joint sites. Expert opinion of the OAGDG panel was used to support recommendations in these instances. However, these guidelines' recommendations pertain to treatment of knee OA specifically, even when making recommendations for individuals with OA in multiple-joint sites. For all considered treatments, best-available evidence of efficacy and safety in knee OA was evaluated.

Our expert panel (OAGDG) represented a range of clinical disciplines that included rheumatologists (NA, FB, GH, DH, KK, TM, FR), orthopedic surgeons (HK, SL), a primary care physician (MU), physical therapists (SBZ, ER), a physiatrist (YH), and a clinical epidemiologist (TM) (Appendix 1). The OAGDG also solicited ongoing input from a patient advocate (RK), who attended the April 2013 OAGDG meeting and provided continuing feedback and oversight *via* the development group's online discussion forum. Our team also included an evidence-based methodologist (RB) who organized the development of the evidence report used by the OAGDG panel. Panel voting was conducted with oversight from OARSI's Ethics Committee. OAGDG members with perceived financial conflicts of interest were recused from voting following written and oral disclosures, with final decisions made by an Ethics Committee representative present at the OAGDG's April 2013 face-to-face meeting. Despite recusals, a majority of practicing clinicians were present within the voting at all times. Thus, the results of voting are unlikely to have lacked sufficient voter expertise for any treatment.

The present statement also incorporated treatments not addressed in the prior OARSI guidelines such as risedronate and duloxetine. Treatments such as ASU, rosehip, electrotherapy, and ultrasound were not included in the 2008 OARSI recommendations but have since been discussed in the 2010 evidence update and assessed within our current guidelines. The present guidelines focused primarily on the non-surgical management of knee OA, though we recommend referral for consideration of orthopedic surgical interventions after more conservative treatment options have been exhausted. To examine the symptomatic slow-acting drug for OA (SYSDOA) effect, glucosamine and chondroitin were assessed separately for disease modification and for symptom relief. Other treatments received one score for overall efficacy, as other treatments were judged to lack sufficient evidence to merit separate assessment for disease modification effect and symptomatic effect.

In comparison to the previous OARSI guidelines published in 2008, recommendations for some treatments have changed. Though the method of assessing treatment appropriateness has changed between guidelines versions, complicating straightforward comparison, it nevertheless appears that recent evidence has increased safety concerns regarding use of treatments such as acetaminophen and opioids (both oral and transdermal), while evidence for use of treatments such as duloxetine, balneotherapy, and land-based exercises such as t'ai chi has strengthened. These differences are updates to previous OARSI guidelines following the development of new treatment options and greater available evidence for existing treatments.

While many of the recommendations in this guidelines statement agree with those published in other OA guidelines, our recommendations differ notably from others in a number of ways. Although our recommendations are based on best-available evidence, the current evidence contains some areas of inconsistency. With regard to non-pharmaceutical treatments, our recommendations were largely similar to other recent guidelines published by the American Academy of Orthopaedic Surgeons (AAOS), ACR, and EULAR, consistently recommending exercise programs for individuals with knee OA as well as weight loss programs for overweight individuals with knee OA. For this guidelines statement, exercise modalities were divided into three groups (land-based, water-based, and strength training) to provide greater specificity than other OA guidelines in assessing their distinct benefits and risks and to evaluate their relative appropriateness for different clinical sub-phenotypes. In other areas of non-pharmacological treatment, our guidelines differed more substantially from others. For electrotherapeutic modalities, AAOS provided an "Inconclusive" recommendation, while these guidelines recommend against the use of TENS and provide an "Uncertain" recommendation for EMG-biofeedback. While ACR conditionally recommends acupuncture for knee OA, and AAOS does not recommend acupuncture, our guidelines provide an "Uncertain" recommendation regarding acupuncture, highlighting the lack of strong available evidence regarding its use. Recommendations regarding biomechanical interventions were also mixed; AAOS provided an inconclusive recommendation regarding force braces, and both AAOS and EULAR recommended against the use of wedged insoles, while ACR conditionally recommended the use of medially wedged insoles. Rather than providing recommendations individually for specific biomechanical modalities, these guidelines recommend the use of biomechanical interventions as directed by an appropriate specialist.

With regard to pharmaceutical treatment modalities, our guidelines also differ from others in several areas. AAOS's 2013 guidelines provided "Inconclusive" recommendations for both acetaminophen and intra-articular corticosteroids, citing for IACS a "lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm." In contrast, our guidelines coincide with ACR's 2012 guidelines in recommending both APAP (for those without relevant co-morbidities) and IACS as appropriate, finding the potential benefits to outweigh associated risks in certain clinical scenarios. Regarding glucosamine and chondroitin, AAOS recommended against use of both treatments and ACR recommended against chondroitin and conditionally against glucosamine. Our guidelines provide greater specificity than previous guidelines by evaluating these treatments separately for symptomatic relief and disease modification. Our group responded more favorably (voting "Uncertain") for the symptomatic efficacy of each of these two treatments than for the disease-modifying use of each (voting "Not appropriate"). The contrasting assessments of glucosamine and chondroitin's symptomatic *versus* disease-modifying efficacy may indicate the source of some of the inconsistency in the perceived value of these treatments among other recent guidelines. Regarding hyaluronic acid treatment, AAOS recommended against the use of IAHA, citing a lack of efficacy. Our guidelines offer a stance similar to that of ACR, providing an "Uncertain" recommendation for IAHA for individuals with knee-only OA. Despite safety and efficacy concerns of IAHA raised by one meta-analysis, a number of analyses revealed positive effect sizes for pain. Oral NSAIDs (both non-selective and COX-2 selective) were conditionally recommended by ACR, which was also reflected in our guidelines through the use of clinical sub-phenotypes. Conversely, AAOS strongly recommended both oral and topical NSAIDs. ACR guidelines conditionally recommend against topical capsaicin use, while we considered it appropriate in patients without relevant co-morbidities. Finally, the ACR provided negative or uncertain recommendations for the use of duloxetine, while these guidelines considered duloxetine appropriate for those without co-morbidities and those with multiple-joint OA and provided an "Uncertain" recommendation for duloxetine in individuals with knee-only OA and co-morbidities.

Limitations of our guidelines include the scope of treatments addressed. These guidelines were developed based on the previous guidelines report and expanded where the OAGDG felt sufficient new evidence was available to merit inclusion (based on number and quality of available trials). Our guidelines did not consider treatments included in the previous OARSI 2010 guidelines such as vitamin E and calcitonin, as well as interventions included in the AAOS guidelines, such as platelet-rich plasma therapy and growth factor injections. Treatment duration and duration of benefit were not voted on separately for limited *versus* extended course for pharmaceutical treatments due to the lack of clarity in available evidence. Other treatments not included in our guidelines include lavage and debridement (considered for inclusion but removed due to consistent evidence of ineffectiveness), strontium (recently received a recommendation to restrict use by the European Medicines Agency and not approved by US FDA)[62], and licofelone (not currently approved by the European Medicines Agency or US FDA). Manual therapy was not included in these guidelines due to insufficient available evidence. Unlike ACR, we did not include patellar taping or psychosocial intervention for knee OA. However, our guidelines also contain many treatment modalities not addressed by other (ACR) guidelines, such as ASU, risedronate, diacerein, and rosehip. In addition, these guidelines divided various treatments (e.g., NSAIDs, opioids, and exercise) into sub-categories to better assess considerations such as delivery method, drug mechanism or other factors, aiming to provide specific and actionable treatment recommendations. Our guidelines are also unique in that the recommendations considered the risk, benefit, and appropriateness of each treatment individually for the specific sub-phenotypes described in our methods. One limitation of these categories is that not every treatment had available research for all clinical sub-phenotypes. In such cases, expert consensus was relied upon *via* the RAND/UCLA voting method. The role of expert opinion and voters' enthusiasm for treatment modalities may also explain some instances where the panel's voting diverged from effect sizes presented in the evidence. The four clinical sub-phenotypes were assessed separately for every treatment considered in order to best capture heterogeneous health profiles and OA disease types.

Conflict of interest

Full disclosure statements from all members of the OARSI Guidelines Development Group are shown in Appendix 1. These were reviewed by the OARSI Ethics Committee. No potential conflicts of interest were identified that should preclude any member of the committee participating in this critical appraisal. No OAGDG members are employees of any pharmaceutical or medical device company. OAGDG members were recused from voting on select treatments where potential conflicts arose, as described in the report Methodology section. Corporate members of OARSI are also listed in Appendix 1. The data extraction team included five members of the Division of Rheumatology, Tufts Medical Center, Boston, MA, USA: Raveendhara Bannuru MD, FAGE, Elizaveta Vaysbrot, MD, Matthew Sullivan, BA, Elena Manning, BS, and Bryan Bourdeau, BS. Dr Bannuru is supported by a F32 HS021396 grant from the Agency for Healthcare Research and Quality. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality. Elizaveta Vaysbrot, Matthew Sullivan, Elena Manning, and Bryan Bourdeau have no conflicts of interest to disclose.

Role of the funding source

These guidelines were commissioned by the OARSI and sponsored by a grant from OARSI. This report is endorsed by the Board of Directors of OARSI; it was developed independently by the OARSI Guidelines Development Group.

Acknowledgments

The authors would like to thank Elizaveta Vaysbrot and Elena Manning for data collection and Diann Stern for logistics support throughout the project. We thank patient representative Robin Katzanek for her guidance. Financial support for data collection at Tufts Medical Center came from an OARSI grant.

Appendix 1

Disclosure of potential conflicts of interest

Name & specialty (in author-list order)	Consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses	Research grants/contracts	Service with organization with interests comparable to OARSI	Recused from voting on the following treatment modalities
T. McAlindon Rheumatologist; Epidemiologist	Flexion Therapeutics|Consulting, Samumed|Consulting, Abbvie|Consulting, Sanofi|Consulting, Myrtus|Licensing fee	NIH, Croma	Co-editor for Arthritis & Rheumatism	Hyaluronic acid
R. Bannuru	None	AHRQ|F32 HS021396 grant	None	Not a voter
M. Sullivan	None	None	None	Not a voter
N. Arden* Rheumatologist	Merck|Consultancy, Roche|Consultancy, Smith and Nephew|Consultancy, Pfizer|Speaker Bureau, Flexion|Consultancy, Bioiberica|Consultancy, Speaker bureau	NIHR|Outcomes of Arthroplasty and Biomedical Research Unit, NIH|Hip morphology, ARUK|VIDEO, project and equipment grants	None	Chondroitin Hyaluronic acid All surgery
F. Berenbaum* Rheumatologist	Pfizer|Advisory board, Expanscience|Advisory board, UCB|Advisory board, Servier|Advisory board, research support,	Agence Nationale Recherche	French Society of Rheumatology	NSAIDs

(*continued on next page*)

Appendix 1 (*continued*)

Name & specialty (in author-list order)	Consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses	Research grants/contracts	Service with organization with interests comparable to OARSI	Recused from voting on the following treatment modalities
	symposium, TRB Chemedica|research support, Sanofi|Advisory board, Abbott|Advisory board			
S. Bierma-Zeinstra* Physical therapist; Epidemiologist	None	Dutch Arthritis Association|research in corticosteroids for OA, OA vascular pathology, early OA diagnosis, brace vs osteotomy treatment, & OA stepped care; The Netherlands Organization for Health Research and Development|research in identification, prevention of knee OA, OA phenotyping, treatment cost-effectiveness (ACL rupture, viscosupplementation, surgery vs conservative treatment in lumbar stenosis), corticosteroids for trochanteric pain syndrome, ankle injury complications, exercise after injury, & exercise therapy for patellofemoral pain syndrome; Nuts Ohra|research in X-ray OA diagnosis, OA pain medication, & statines & OA; EU FP7|markers for early detection & progression of OA	None	Glucosamine
S. Bierma-Zeinstra (disclosure cont'd)				
G. Hawker* Rheumatologist	Women's College Hospital|Physician in Chief of Medicine|Salary Support Award, Women's College Hospital Foundation|FM Hill Chair in Academic Women's Medicine. *Nothing to declare*	Operating grants from the Canadian Institutes of Health Research|Canadian Arthritis Network|Cochrane Collaboration/writing paper with Adelphi, a marketing company who worked for Pfizer on a survey of physicians regarding factors that influence their perceptions of OA severity – unpaid	None	None
Y. Henrotin* Physical therapy & rehabilitation	Bioiberica; BioXtract; Danone; Nestle; Pierre Fabre; Grunenthal; Expanscience; Artialis; Tilman; Merck; Ibsa|Honoraria. Patent ownership: Artialis|Biomarkers; Kit immunoassays| Development & commercialization of biomarkers of cartilage degradation & inflammation	Walloon Government-Belgium|First Post-Doc RW/ 5291 PROMART-Recherche de nouveaux biomarqueurs (2007–2009).165.765; First Post-Doc RW/716609 CARTIMAT: Recherche de nouveaux biomateriaux; FIRST Entreprise - 73.726,4 Euros, European commission|FP7 D-Board, rd; Bioiberica & Expanscience|unrestricted educational grants	None	Chondroitin
D. Hunter* Rheumatologist	DonJoy|Royalties; Merck Serono|Consulting, Flexion Therapeutics|Consulting	Australian Research Council|Future Fellowship, NIH|POMA, NHMRC|project grants	Bone and Joint Decade International Coordinating Council, Advisory editor for Arthritis Care and Research, Associate Editor for International Journal of Rheumatic Diseases	Biomechanical interventions
H. Kawaguchi* Orthopedic surgeon	Teijin Pharma Co., Ltd.|Consulting fee	None	BMC Musculoskeletal Disorders|Associate Editor, Japanese Orthopaedic Association|Committee Member, Japanese Society for Bone and Mineral Metabolism|Committee Member, Journal of	Hyaluronic acid

Appendix 1 (*continued*)

Name & specialty (in author-list order)	Consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses	Research grants/contracts	Service with organization with interests comparable to OARSI	Recused from voting on the following treatment modalities
			Orthopaedic Science|Editorial Board, Journal of Bone &Mineral Metabolism|Editorial Board, Japanese Society of Cartilage Metabolism|Comm. Member	
R. Katzanek Patient advocate	Nothing to declare	None	None	N/A
K. Kwoh Rheumatologist	Novartis|Advisory Board and DSMB, NIH|DSMB, Express Scripts|Consulting, Pfizer|RA Quality Measures Roundtable	NIH|NIAMS P60AR054731 PITT-MCRC for rheumatic and musculoskeletal diseases; NIAMS N01AR-2-2260 Clinical centers for the Osteoarthritis Initiative; NHLBI HHSN26820100002 Pivotal OAI MRI Analyses (POMA); NIAMS R01AR056630 Single- vs Double-Bundle ACL Reconstruction: A Prospective Randomized Trial; NINR R01NR010904 Promoting Physical Activity in Older Adults with Co-morbidity; CDC|U48DP001918 Health Promotion and Disease Prevention Research Center	Arthritis Foundation|Public Health Committee	Glucosamine Risedronate
S. Lohmander* Orthopedic surgeon	Merck Serono|Advisory board, Informed Medical Decision Making|Speaker honorarium, Össur Advisory Board, Abbott Consultancy, Flexion Therapeutics Advisory Board, Allergan Consultancy, Medivir Consultancy, Merrimack Pharmaceuticals Consultancy, Servier Consultancy	Swedish Research Council|Lund University, Swedish Rheumatism Association|Lund University, Medical faculty|Lund University	None	Biomechanical interventions
F. Rannou* Rheumatologist	Sanofi Aventis, Pfizer, Rottapharm, Pierre Fabre, Genzyme, Merck, Genévrier, Expanscience, Negma, Servier|Consulting/ Advisory board	AP-HP|Non-pharmacological treatments in rheumatic diseases, GSK|HO-1 inducer molecules in cartilage, Fondation de l'Avenir|Molecular mapping of IVD in scoliosis	Member of the Eular Scientific Committee	NSAIDs Hyaluronic acid ASU Diacerein
E. Roos* Physical therapist	National Welfare Board, Sweden|Reviewer, National board for preventive medicine, Denmark|Board member, Össur|Lecture fees, Finnish Orthopedic Society|Lecture fees, Studentlitteratur|Royalties, Munksgaard|Royalties, Osteoarthritis and Cartilage|Associate Editor	Southern Health Care Region, Denmark|RCT on exercise vs pharma, Danish Rheumatism Association|Knee OA prevention and treatment	None	None
M. Underwood Primary care practitioner; primary care research	Travel, Accommodation and Conference fee waiver from OARSI to attend OAGDG meetings concurrent with annual scientific meeting	NIHR Programme grants|Improving outcomes from the treatment of back pain; Improving self-management of chronic pain, NHS HTA Programme|Prevention of Fall Injury Trial (Pre-FIT); Adherence to strengthening activities in rheumatoid arthritis of the hand (SARAH); Older People's Exercise intervention in Residential and nursing Accommodation	National Institute for Health and Care Excellence (NICE)| Chair of Headache Guideline Development Group (2010–12). Chair NICE Accreditation Advisory Committee (2013) NICE Strategy Board, in attendance (2013)	Acupuncture

(*continued on next page*)

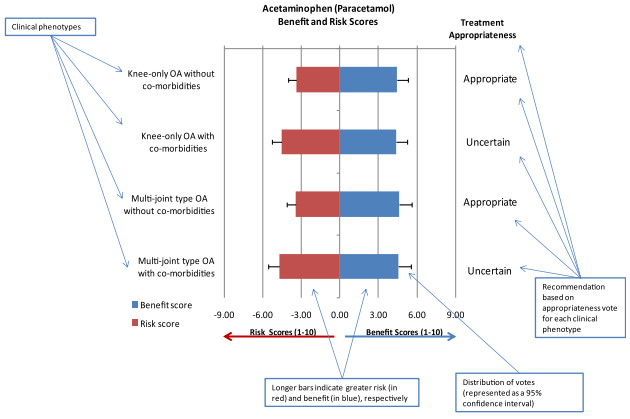
Appendix 1 (*continued*)

Name & specialty (in author-list order)	Consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses	Research grants/contracts	Service with organization with interests comparable to OARSI	Recused from voting on the following treatment modalities
		(OPERA), National Centre for Osteopathic Research|Investigating osteopath's attitudes to managing and assessing risk in clinical settings and patient's experiences and responses, Research for Patient Benefit|Improving Patient Choice in Treating Low Back Pain (IMPACT - LBP). NHS Health Technology Assessment Programme. Facet joint feasibility study.		

OARSI's Congress sponsors and corporate members for 2013 include the following: Bioiberica; EMD Serono; Expanscience; Rottapharm/Madaus; Abbvie; Astellas; Bioventus; Boston Imaging Core Lab (BICL); Chondrometrics; Fidia Pharma USA, Inc.; Flexion; Perceptive Informatics; Merck; Seikagaku; Servier; Zimmer. No direct medical industry support was used or requested for guideline development. Guidelines development was a budgeted item in OARSI's annual budget.

* Panel member has an editorial position with the Osteoarthritis and Cartilage journal.

Appendix 2



Appendix 3

Table A
Appropriateness voting data

		Appropriateness scores					
		No co-morbidities			Co-morbidities		
		Median	Appropriate (Y/N/U)	Disagreement?	Median	Appropriate (Y/N/U)	Disagreement?
Non-pharmaceutical treatments							
Acupuncture	Knee	5	Uncertain	No	4.5	Uncertain	No
	Multi-joint	4.5	Uncertain	No	4.5	Uncertain	No
Balneotherapy	Knee	5	Uncertain	No	6	Uncertain	No
	Multi-joint	6	Uncertain	No	7	Yes	No
Biomechanical interventions	Knee	7	Yes	No	7	Yes	No
	Multi-joint	7	Yes	No	7	Yes	No
Cane (walking stick)	Knee	7	Yes	No	7	Yes	No
	Multi-joint	6	Uncertain	No	6	Uncertain	No
Crutches	Knee	6	Uncertain	No	6	Uncertain	No
	Multi-joint	5	Uncertain	No	5.5	Uncertain	No
Electrotherapy/neuromuscular electrical stimulation	Knee	3	No	No	3	No	No

Table A (*continued*)

		Appropriateness scores					
		No co-morbidities			Co-morbidities		
		Median	Appropriate (Y/N/U)	Disagreement?	Median	Appropriate (Y/N/U)	Disagreement?
	Multi-joint	3	No	No	3	No	No
Exercise (land-based)	Knee	8	Yes	No	8	Yes	No
	Multi-joint	8	Yes	No	8	Yes	No
Exercise (water-based)	Knee	7	Yes	No	7	Yes	No
	Multi-joint	8	Yes	No	8	Yes	No
Strength training	Knee	8	Yes	No	8	Yes	No
	Multi-joint	8	Yes	No	7	Yes	No
Self-management and education	Knee	8	Yes	No	9	Yes	No
	Multi-joint	9	Yes	No	9	Yes	No
TENS	Knee	5	Uncertain	No	5	Uncertain	No
	Multi-joint	3	No	No	3	No	No
Weight management	Knee	8	Yes	No	8	Yes	No
	Multi-joint	8	Yes	No	9	Yes	No
Ultrasound	Knee	4	Uncertain	No	4	Uncertain	No
	Multi-joint	3	No	No	3	No	No
Pharmaceutical treatments							
Acetaminophen (paracetamol)	Knee	7	Yes	No	6	Uncertain	No
	Multi-joint	7	Yes	No	6	Uncertain	No
ASU	Knee	4	Uncertain	No	4	Uncertain	No
	Multi-joint	5	Uncertain	No	5	Uncertain	No
Capsaicin	Knee	7	Yes	No	6	Uncertain	No
	Multi-joint	6	Uncertain	No	6	Uncertain	No
Corticosteriods (intra-articular injection)	Knee	7	Yes	No	7	Yes	No
	Multi-joint	7	Yes	No	7	Yes	No
Chondroitin: symptom relief	Knee	5	Uncertain	No	5	Uncertain	No
	Multi-joint	5	Uncertain	No	5	Uncertain	No
Chondroitin: disease modification	Knee	3	No	No	3	No	No
	Multi-joint	3	No	No	3	No	No
Diacerein	Knee	4	Uncertain	No	4	Uncertain	No
	Multi-joint	4	Uncertain	No	4	Uncertain	No
Duloxetine	Knee	7	Yes	No	6	Uncertain	No
	Multi-joint	7	Yes	No	7	Yes	No
Glucosamine: symptom relief	Knee	5.5	Uncertain	No	5.5	Uncertain	No
	Multi-joint	5.5	Uncertain	No	5.5	Uncertain	No
Glucosamine: disease modification	Knee	3	No	No	3	No	No
	Multi-joint	3	No	No	3	No	No
Hyaluronic acid (intra-articular injection)	Knee	5	Uncertain	No	4	Uncertain	No
	Multi-joint	3	No	No	3	No	No
NSAIDs (topical)	Knee	8	Yes	No	7	Yes	No
	Multi-joint	6	Uncertain	No	6	Uncertain	No
Opioids: transdermal	Knee	4	Uncertain	No	4	Uncertain	No
	Multi-joint	5	Uncertain	No	4	Uncertain	No
Opioids: oral	Knee	5	Uncertain	No	4	Uncertain	No
	Multi-joint	5	Uncertain	No	6	Uncertain	No
Risedronate	Knee	3	No	No	3	No	No
	Multi-joint	3	No	No	3	No	No
Rosehip	Knee	5	Uncertain	No	5	Uncertain	No
	Multi-joint	5	Uncertain	No	5	Uncertain	No

For each treatment modality, the OAGDG voted on appropriateness using a nine-point scale (1–9).
Definitions: **No co-morbidities**: The individual with OA has no pertinent co-morbid health concerns. **Co-morbidities**: The individual with OA has any of the following pertinent co-morbid health concerns: diabetes; hypertension; CV disease; renal failure; GI bleeding; depression; or physical impairment limiting activity, including obesity. **Knee**: Symptomatic OA in one or both knees only. **Multi-joint OA**: Symptomatic OA of the knee(s) in addition to other joints (e.g., hip, hand, spine, etc).
Disagreement: An appropriateness vote was considered to be in 'disagreement' if greater than one-third of votes fell in the opposite tertile to the median score [e.g., a vote was considered in "Disagreement" if it received an "Appropriate" median vote ($\geq$7) with five of 13 members voting "Not appropriate" ($\leq$3)].

Table B
Risk scores, benefit scores, and composite risk and benefit scores

		Risk scores		Benefit scores		Benefit and risk scores	
		No co-morbidities	Co-morbidities	No co-morbidities	Co-morbidities	No co-morbidities	Co-morbidities
		Mean (1–10)	Mean (1–10)	Mean (1–10)	Mean (1–10)	(1–100)	(1–100)
Non pharmaceutical treatments							
Acupuncture	Knee	1.9	2.3	3.1	3.0	28.0	26.3
	Multi-joint	1.9	2.3	3.1	3.0	28.0	26.3
Balneotherapy	Knee	1.3	1.5	4.2	4.2	40.3	40.0
	Multi-joint	1.3	1.6	4.5	4.5	43.2	41.9
Biomechanical interventions	Knee	1.5	2.0	5.6	5.6	57.0	50.4

(*continued on next page*)

Table B (*continued*)

		Risk scores		Benefit scores		Benefit and risk scores	
		No co-morbidities	Co-morbidities	No co-morbidities	Co-morbidities	No co-morbidities	Co-morbidities
		Mean (1–10)	Mean (1–10)	Mean (1–10)	Mean (1–10)	(1–100)	(1–100)
	Multi-joint	1.6	2.1	4.7	4.7	37.6	41.8
Cane (walking stick)	Knee	1.6	1.6	5.0	5.0	46.9	46.9
	Multi-joint	1.8	1.8	4.2	4.0	38.3	36.9
Crutches	Knee	1.7	1.7	4.4	4.3	40.8	40.1
	Multi-joint	1.8	1.8	3.7	3.8	33.8	34.5
Electrotherapy/neuromuscular electrical stimulation	Knee	2.0	2.1	2.5	2.4	22.2	21.3
	Multi-joint	2.0	2.1	1.9	1.9	17.3	17.2
Exercise (land-based)	Knee	1.2	1.9	6.6	6.8	64.6	61.4
	Multi-joint	1.3	2.1	6.4	6.5	61.9	58.3
Exercise (water-based)	Knee	1.5	2.3	5.9	6.2	56.0	54.2
	Multi-joint	1.5	2.2	6.2	6.5	59.0	56.7
Strength training	Knee	1.4	1.8	6.9	6.8	66.6	62.0
	Multi-joint	1.6	2.2	6.0	6.0	56.3	53.1
Self management and education	Knee	1.2	1.5	4.9	5.1	48.1	48.4
	Multi-joint	1.2	1.5	5.2	5.2	50.3	49.5
TENS	Knee	1.8	1.8	3.2	3.2	29.1	28.9
	Multi-joint	1.8	1.8	2.4	2.4	22.0	21.8
Weight management	Knee	1.2	1.5	6.1	6.3	59.4	60.2
	Multi-joint	1.2	1.5	6.2	6.4	60.1	60.4
Ultrasound	Knee	1.3	1.5	2.8	3.0	27.6	28.6
	Multi-joint	1.4	1.4	2.4	2.5	22.9	24.4
Pharmaceutical treatments							
Acetaminophen (paracetamol)	Knee	3.4	4.5	4.5	4.4	34.0	28.3
	Multi-joint	3.5	4.7	4.6	4.5	34.8	28.6
Avocado soybean unsaponfiables	Knee	1.6	1.8	3.5	3.5	33.2	32.6
	Multi-joint	1.6	1.8	3.6	3.6	34.0	33.4
Capsaicin	Knee	2.6	2.8	5.1	5.1	42.6	41.8
	Multi-joint	2.9	3.1	4.7	4.7	37.9	37.2
Corticosteriods (intra-articular injection)	Knee	2.8	3.6	6.5	6.4	53.8	47.1
	Multi-joint	2.8	3.6	5.2	5.3	42.7	39.2
Chondroitin: symptom relief	Knee	1.1	1.3	3.8	3.9	37.8	38.0
	Multi-joint	1.1	1.3	3.8	4.0	37.8	38.9
Chondroitin: disease modification	Knee	1.1	1.3	2.7	2.7	27.0	26.5
	Multi-joint	1.1	1.4	2.6	2.5	26.1	23.7
Diacerein	Knee	3.8	4.0	3.7	3.7	26.6	25.7
	Multi-joint	3.8	4.0	3.8	3.8	27.8	26.3
Duloxetine	Knee	4.0	4.7	5.3	5.4	37.2	34.0
	Multi-joint	4.0	4.7	5.6	5.6	39.3	35.4
Glucosamine: symptom relief	Knee	1.4	1.7	3.9	3.9	37.4	36.3
	Multi-joint	1.5	1.7	4.0	4.0	38.0	37.2
Glucosamine: disease modification	Knee	1.4	1.7	2.7	2.7	26.3	25.3
	Multi-joint	1.4	1.7	2.5	2.5	24.5	23.6
Hyaluronic acid (intra-articular injection)	Knee	3.1	3.8	4.1	4.2	32.4	30.5
	Multi-joint	3.3	3.9	3.0	3.1	23.0	22.1
NSAIDs (topical)	Knee	2.7	3.5	6.0	5.9	49.8	44.7
	Multi-joint	2.9	3.8	5.2	5.2	42.2	36.9
Opioids: transdermal	Knee	4.8	6.1	5.2	4.9	31.7	24.2
	Multi-joint	4.9	6.1	5.3	5.1	32.3	25.0
Opioids: oral	Knee	5.5	6.5	5.6	5.4	30.7	24.0
	Multi-joint	5.6	6.5	5.7	5.4	30.7	24.0
Risedronate	Knee	3.2	3.3	2.7	2.7	20.9	20.4
	Multi-joint	3.2	3.3	2.8	2.7	21.5	20.4
Rosehip	Knee	1.8	1.9	3.3	3.4	30.3	30.7
	Multi-joint	1.8	1.9	3.3	3.4	30.3	30.7

For each treatment modality, the OAGDG voted on therapeutic benefit on a 10-point scale (1–10) and overall risk on a 10-point scale (1–10). The composite benefit and risk score is the product of the benefit score (1–10) and the transposed risk score (where 1 = highest and 10 = safety) yielding a range of 1 (worst) to 100 (best).
No co-morbidities: The individual with OA has no pertinent co-morbid health concerns. **Co-morbidities:** The individual with OA has any of the following pertinent co-morbid health concerns: diabetes; hypertension; cardiovascular disease; renal failure; GI bleeding; depression; or physical impairment limiting activity, including obesity. **Knee:** Symptomatic OA in one or both knees only. **Multi-joint:** Symptomatic OA of the knee(s) in addition to other joints (e.g. hip, hand, spine, etc).

Table C
Oral NSAIDs voting data

Treatment	OA type	Appropriateness vote			Voting disagreement?			Percent voting in favor of gastroprotection		
		Co-morbidity risk			Co-morbidity risk			Co-morbidity risk		
		No co-morbidities	Moderate risk	High risk	No co-morbidities	Moderate risk	High risk	No co-morbidities	Moderate risk	High risk
Oral NSAIDs (non-selective)	Knee-only OA	7.0	5.0	2.0	No	No	No	33%	92%	100%
	Multi-joint OA	7.5	4.0	2.0	No	No	No	67%	92%	92%

Table C (*continued*)

Treatment	OA type	Appropriateness vote			Voting disagreement?			Percent voting in favor of gastroprotection		
		Co-morbidity risk			Co-morbidity risk			Co-morbidity risk		
		No co-morbidities	Moderate risk	High risk	No co-morbidities	Moderate risk	High risk	No co-morbidities	Moderate risk	High risk
Oral NSAIDs (COX-2 inhibitors)	Knee-only OA	7.0	6.0	3.0	No	No	No	18%	50%	100%
	Multi-joint OA	7.0	7.0	3.0	No	No	No	36%	50%	91%
Treatment	OA Type	Risk scores			Benefit scores			Benefit and risk scores		
		Co-morbidity risk			Co-morbidity risk			Co-morbidity risk		
		No co-morbidities	Moderate risk	High risk	No co-morbidities	Moderate risk	High risk	No co-morbidities	Moderate risk	High risk
Oral NSAIDs (non-selective)	Knee-only OA	4.6	6.1	7.8	5.9	5.6	5.2	40.7	29.7	17.3
	Multi-joint OA	4.6	6.1	7.8	6.2	5.6	5.3	42.8	30.9	18.6
Oral NSAIDs (COX-2 inhibitors)	Knee-only OA	4.6	6.1	6.6	6.0	5.7	5.4	46.6	38.3	24.7
	Multi-joint OA	3.8	4.7	6.6	6.4	6.1	5.8	46.8	38.8	25.4

For each treatment modality, the OAGDG voted on appropriateness using a nine-point scale (1–9), on therapeutic benefit on a 10-point scale (1–10) and overall risk on a 10-point scale (1–10). The composite benefit and risk score is the product of the benefit score (1–10) and the transposed risk score (where 1 = highest and 10 = safety) yielding a range of 1 (worst) to 100 (best).

Definitions: **No co-morbidities**: The individual with OA has no pertinent co-morbid health concerns. **Co-morbidities**: The individual with OA has any of the following pertinent co-morbid health concerns: diabetes; hypertension; CV disease; renal failure; GI bleeding; depression; or physical impairment limiting activity, including obesity. **Knee-only OA**: Symptomatic OA in one or both knees only. **Multi-joint OA**: Symptomatic OA of the knee(s) in addition to other joints (e.g., hip, hand, spine, etc).

Disagreement: An appropriateness vote was considered to be in 'disagreement' if greater than one-third of votes fell in the opposite tertile to the median score [e.g., a vote was considered in "Disagreement" if it received an "Appropriate" median vote (≥7) with five of 13 members voting "Not appropriate" (≤3)].

References

1. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, *et al*. OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis and Cartilage/OARS, Osteoarthritis Research Society 2010;18(4):476–99. Epub 2010/02/23. http://dx.doi.org/10.1016/j.joca.2010.01.013. PubMed PMID: 20170770.
2. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, *et al*. OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis and Cartilage/OARS, Osteoarthritis Research Society 2008;16(2):137–62. Epub 2008/02/19. http://dx.doi.org/10.1016/j.joca.2007.12.013. PubMed PMID: 18279766.
3. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, *et al*. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthritis and Cartilage/OARS, Osteoarthritis Research Society 2007;15(9):981–1000. Epub 2007/08/28. http://dx.doi.org/10.1016/j.joca.2007.06.014. PubMed PMID: 17719803.
4. Fitch K, Bernstein S, Aguilar MD, Burnand B, LaCalle JR, Lazaro P, *et al*. The RAND/UCLA Appropriateness Method User's Manual. Santa Monica: Rand; 2001.
5. Manheimer E, Cheng K, Linde K, Lao L, Yoo J, Wieland S, *et al*. Acupuncture for peripheral joint osteoarthritis. Cochrane Database Syst Rev 2010;(1):CD001977. Epub 2010/01/22. http://dx.doi.org/10.1002/14651858.CD001977.pub2. PubMed PMID: 20091527; PubMed Central PMCID: PMCPMC3169099.
6. Falagas ME, Zarkadoulia E, Rafailidis PI. The therapeutic effect of balneotherapy: evaluation of the evidence from randomised controlled trials. Int J Clin Pract 2009;63(7):1068–84. Epub 2009/07/03. http://dx.doi.org/10.1111/j.1742-1241.2009.02062.x. PubMed PMID: 19570124.
7. Harzy T, Ghani N, Akasbi N, Bono W, Nejjari C. Short- and long-term therapeutic effects of thermal mineral waters in knee osteoarthritis: a systematic review of randomized controlled trials. Clin Rheumatol 2009;28(5):501–7. Epub 2009/02/20. http://dx.doi.org/10.1007/s10067-009-1114-2. PubMed PMID: 19225707.
8. Sherman G, Zeller L, Avriel A, Friger M, Harari M, Sukenik S. Intermittent balneotherapy at the Dead Sea area for patients with knee osteoarthritis. Isr Med Assoc J: IMAJ 2009;11(2):88–93. Epub 2009/05/13. PubMed PMID: 19432036.
9. Forestier R, Desfour H, Tessier JM, Francon A, Foote AM, Genty C, *et al*. Spa therapy in the treatment of knee osteoarthritis: a large randomised multicentre trial. Ann Rheum Dis 2010;69(4):660–5. Epub 2009/09/08. http://dx.doi.org/10.1136/ard.2009.113209. PubMed PMID: 19734131; PubMed Central PMCID: PMCPMC2927613.
10. Raja K, Dewan N. Efficacy of knee braces and foot orthoses in conservative management of knee osteoarthritis: a systematic review. Am J Phys Med Rehabil/Assoc Acad Physiatr 2011;90(3):247–62. Epub 2011/01/29. http://dx.doi.org/10.1097/PHM.0b013e318206386b. PubMed PMID: 21273902.
11. Bennell KL, Bowles KA, Payne C, Cicuttini F, Williamson E, Forbes A, *et al*. Lateral wedge insoles for medial knee osteoarthritis: 12 month randomised controlled trial. BMJ (Clinical Research Ed) 2011;342:d2912. Epub 2011/05/20. http://dx.doi.org/10.1136/bmj.d2912. PubMed PMID: 21593096; PubMed Central PMCID: PMCPMC3100910.
12. van Raaij TM, Reijman M, Brouwer RW, Bierma-Zeinstra SM, Verhaar JA. Medial knee osteoarthritis treated by insoles or braces: a randomized trial. Clin Orthop Relat Res 2010;468(7):1926–32. Epub 2010/02/24. http://dx.doi.org/10.1007/s11999-010-1274-z. PubMed PMID: 20177839; PubMed Central PMCID: PMCPMC2881986.
13. Erhart JC, Mundermann A, Elspas B, Giori NJ, Andriacchi TP. Changes in knee adduction moment, pain, and functionality with a variable-stiffness walking shoe after 6 months. J Orthop Res: Off Publ Orthop Res Soc 2010;28(7):873–9. Epub 2010/01/09. http://dx.doi.org/10.1002/jor.21077. PubMed PMID: 20058261.
14. Jones A, Silva PG, Silva AC, Colucci M, Tuffanin A, Jardim JR, *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;71(2):172–9. Epub 2011/12/01. http://dx.doi.org/10.1136/ard.2010.140178. PubMed PMID: 22128081.
15. Giggins O, Fullen B, Coughlan G. Neuromuscular electrical stimulation in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Clin Rehabil 2012;26(10):867–81. Epub 2012/02/11. http://dx.doi.org/10.1177/0269215511431902. PubMed PMID: 22324059.
16. Yilmaz OO, Senocak O, Sahin E, Baydar M, Gulbahar S, Bircan C, *et al.* Efficacy of EMG-biofeedback in knee osteoarthritis. Rheumatol Int 2010;30(7):887–92. Epub 2009/08/21. http://dx.doi.org/10.1007/s00296-009-1070-9. PubMed PMID: 19693508.
17. Jansen MJ, Viechtbauer W, Lenssen AF, Hendriks EJ, de Bie RA. Strength training alone, exercise therapy alone, and exercise therapy with passive manual mobilisation each reduce pain and disability in people with knee osteoarthritis: a systematic review. J Physiother 2011;57(1):11–20. Epub 2011/03/16. http://dx.doi.org/10.1016/s1836-9553(11)70002-9. PubMed PMID: 21402325.
18. Iversen MD. Rehabilitation interventions for pain and disability in osteoarthritis: a review of interventions including exercise, manual techniques, and assistive devices. Orthop Nurs/Natl Assoc Orthop Nurses 2012;31(2):103–8. Epub 2012/03/27. http://dx.doi.org/10.1097/NOR.0b013e31824fce07. PubMed PMID: 22446803.
19. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S. Does land-based exercise reduce pain and disability associated with hip osteoarthritis? A meta-analysis of randomized controlled trials. Osteoarthritis and Cartilage/OARS,. Osteoarthritis Research Society 2010;18(5):613–20. Epub 2010/03/02. http://dx.doi.org/10.1016/j.joca.2010.01.003. PubMed PMID: 20188228.
20. Fransen M, McConnell S. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev 2008;(4):CD004376. Epub 2008/10/10. http://dx.doi.org/10.1002/14651858.CD004376.pub2. PubMed PMID: 18843657.
21. Bannuru RR, Abariga S, Wang C. How effective is tai chi mind-body therapy for knee osteoarthritis? A systematic review and meta-analysis. Osteoarthritis Research Society International World Congress; 2012 Apr 26–29; Barcelona, Spain. Osteoarthritis Cartilage 2012;20(Suppl 1):S281–2.
22. Kang JW, Lee MS, Posadzki P, Ernst E. T'ai chi for the treatment of osteoarthritis: a systematic review and meta-analysis. BMJ Open 2011;1(1):e000035. Epub 2011/10/25. http://dx.doi.org/10.1136/bmjopen-2010-000035. PubMed PMID: 22021734; PubMed Central PMCID: PMCPMC3191392.
23. Bartels EM, Lund H, Hagen KB, Dagfinrud H, Christensen R, Danneskiold-Samsoe B. Aquatic exercise for the treatment of knee and hip osteoarthritis. Cochrane Database Syst Rev 2007;(4):CD005523. Epub 2007/10/19. http://dx.doi.org/10.1002/14651858.CD005523.pub2. PubMed PMID: 17943863.
24. Du S, Yuan C, Xiao X, Chu J, Qiu Y, Qian H. Self-management programs for chronic musculoskeletal pain conditions: a systematic review and meta-analysis. Patient Educ Couns 2011;85(3):e299–310. Epub 2011/04/05. http://dx.doi.org/10.1016/j.pec.2011.02.021. PubMed PMID: 21458196.
25. Chondosh J, Morton SC, Mojica W, Maglione M, Suttorp MJ, Hilton L, *et al.* Meta-analysis: chronic disease self-management programs for older adults. Ann Intern Med 2005;143(6):427–38. Epub 2005/09/21. PubMed PMID: 16172441.
26. Ravaud P, Flipo RM, Boutron I, Roy C, Mahmoudi A, Giraudeau B, *et al.* ARTIST (osteoarthritis intervention standardized) study of standardised consultation versus usual care for patients with osteoarthritis of the knee in primary care in France: pragmatic randomised controlled trial. BMJ (Clinical Research Ed) 2009;338:b421. Epub 2009/02/25. http://dx.doi.org/10.1136/bmj.b421. PubMed PMID: 19237406; PubMed Central PMCID: PMCPMC2651104.
27. Hurley MV, Walsh NE, Mitchell H, Nicholas J, Patel A. Long-term outcomes and costs of an integrated rehabilitation program for chronic knee pain: a pragmatic, cluster randomized, controlled trial. Arthritis Care Res 2012;64(2):238–47. Epub 2011/09/29. http://dx.doi.org/10.1002/acr.20642. PubMed PMID: 21954131.
28. Hansson EE, Jonsson-Lundgren M, Ronnheden AM, Sorensson E, Bjarnung A, Dahlberg LE. Effect of an education programme for patients with osteoarthritis in primary care–a randomized controlled trial. BMC Musculoskelet Disord 2010;11:244. Epub 2010/10/26. http://dx.doi.org/10.1186/1471-2474-11-244. PubMed PMID: 20969809; PubMed Central PMCID: PMCPMC2987970.
29. Allen KD, Oddone EZ, Coffman CJ, Datta SK, Juntilla KA, Lindquist JH, *et al.* Telephone-based self-management of osteoarthritis: a randomized trial. Ann Intern Med 2010;153(9):570–9. Epub 2010/11/03. http://dx.doi.org/10.7326/0003-4819-153-9-201011020-00006, http://dx.doi.org/10.1059/0003-4819-153-9-201011020-00006. PubMed PMID: 21041576.
30. Ackerman IN, Buchbinder R, Osborne RH. Challenges in evaluating an Arthritis Self-Management Program for people with hip and knee osteoarthritis in real-world clinical settings. J Rheumatol 2012;39(5):1047–55. Epub 2012/03/03. http://dx.doi.org/10.3899/jrheum.111358. PubMed PMID: 22382340.
31. Rutjes AW, Nuesch E, Sterchi R, Kalichman L, Hendriks E, Osiri M, *et al.* Transcutaneous electrostimulation for osteoarthritis of the knee. Cochrane Database Syst Rev 2009;(4):CD002823. Epub 2009/10/13. http://dx.doi.org/10.1002/14651858.CD002823.pub2. PubMed PMID: 19821296.
32. Atamaz FC, Durmaz B, Baydar M, Demircioglu OY, Iyiyapici A, Kuran B, *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;93(5):748–56. Epub 2012/03/31. http://dx.doi.org/10.1016/j.apmr.2011.11.037. PubMed PMID: 22459699.
33. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis 2007;66(4):433–9. Epub 2007/01/06. http://dx.doi.org/10.1136/ard.2006.065904. PubMed PMID: 17204567; PubMed Central PMCID: PMCPMC1856062.
34. Rutjes AW, Nuesch E, Sterchi R, Juni P. Therapeutic ultrasound for osteoarthritis of the knee or hip. Cochrane Database Syst Rev 2010;(1):CD003132. Epub 2010/01/22. http://dx.doi.org/10.1002/14651858.CD003132.pub2. PubMed PMID: 20091539.
35. Loyola-Sanchez A, Richardson J, MacIntyre NJ. Efficacy of ultrasound therapy for the management of knee osteoarthritis: a systematic review with meta-analysis. Osteoarthritis and Cartilage/OARS, Osteoarthritis Research Society 2010;18(9):1117–26. Epub 2010/07/20. http://dx.doi.org/10.1016/j.joca.2010.06.010. PubMed PMID: 20637297.
36. Ulus Y, Tander B, Akyol Y, Durmus D, Buyukakincak O, Gul U, *et al.* Therapeutic ultrasound versus sham ultrasound for the management of patients with knee osteoarthritis: a randomized double-blind controlled clinical study. Int J Rheum Dis 2012;15(2):197–206. Epub 2012/04/03. http://dx.doi.org/10.1111/j.1756-185X.2012.01709.x. PubMed PMID: 22462424.

37. Bannuru RRDU, McAlindon TE. Reassessing the role of acetaminophen in osteoarthritis: systematic review and meta-analysis. Osteoarthritis Research Society International World Congress; 2010 Sep 23–26; Brussels, Belgium. Osteoarthritis Cartilage 2010;18(Suppl 2):S250.
38. Craig DG, Bates CM, Davidson JS, Martin KG, Hayes PC, Simpson KJ. Staggered overdose pattern and delay to hospital presentation are associated with adverse outcomes following paracetamol-induced hepatotoxicity. Br J Clin Pharmacol 2012;73(2):285–94.
39. Christensen R, Bartels EM, Astrup A, Bliddal H. Symptomatic efficacy of avocado-soybean unsaponifiables (ASU) in osteoarthritis (OA) patients: a meta-analysis of randomized controlled trials. Osteoarthritis and Cartilage/OARS, Osteoarthritis Research Society 2008;16(4):399–408. Epub 2007/11/29. http://dx.doi.org/10.1016/j.joca.2007.10.003. PubMed PMID: 18042410.
40. Mason L, Moore RA, Derry S, Edwards JE, McQuay HJ. Systematic review of topical capsaicin for the treatment of chronic pain. BMJ (Clinical Research Ed) 2004;328(7446):991. Epub 2004/03/23. http://dx.doi.org/10.1136/bmj.38042.506748.EE. PubMed PMID: 15033881; PubMed Central PMCID: PMCPMC404499.
41. Kosuwon W, Sirichatiwapee W, Wisanuyotin T, Jeeravipoolvarn P, Laupattarakasem W. Efficacy of symptomatic control of knee osteoarthritis with 0.0125% of capsaicin versus placebo. J Med Assoc Thai = Chotmaihet Thangphaet 2010;93(10):1188–95. Epub 2010/10/27. PubMed PMID: 20973322.
42. Chou R, McDonagh MS, Nakamoto E, Griffin J. Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review. Rockville MD 2011 Oct.
43. Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Arthritis Rheum 2009;61(12):1704–11. Epub 2009/12/02. http://dx.doi.org/10.1002/art.24925. PubMed PMID: 19950318.
44. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006;(2):CD005328. Epub 2006/04/21. http://dx.doi.org/10.1002/14651858.CD005328.pub2. PubMed PMID: 16625636.
45. Wandel S, Juni P, Tendal B, Nuesch E, Villiger PM, Welton NJ, *et al*. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. BMJ (Clinical Research Ed) 2010;341:c4675. Epub 2010/09/18. http://dx.doi.org/10.1136/bmj.c4675. PubMed PMID: 20847017; PubMed Central PMCID: PMCPMC2941572.
46. Reichenbach S, Sterchi R, Scherer M, Trelle S, Burgi E, Burgi U, *et al*. Meta-analysis: chondroitin for osteoarthritis of the knee or hip. Ann Intern Med 2007;146(8):580–90. Epub 2007/04/18. PubMed PMID: 17438317.
47. Hochberg MC, Zhan M, Langenberg P. The rate of decline of joint space width in patients with osteoarthritis of the knee: a systematic review and meta-analysis of randomized placebo-controlled trials of chondroitin sulfate. Curr Med Res Opin 2008;24(11):3029–35. Epub 2008/10/02. http://dx.doi.org/10.1185/03007990802434932. PubMed PMID: 18826751.
48. Lee YH, Woo JH, Choi SJ, Ji JD, Song GG. Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis. Rheumatol Int 2010;30(3):357–63. Epub 2009/06/23. http://dx.doi.org/10.1007/s00296-009-0969-5. PubMed PMID: 19544061.
49. Bartels EM, Bliddal H, Schondorff PK, Altman RD, Zhang W, Christensen R. Symptomatic efficacy and safety of diacerein in the treatment of osteoarthritis: a meta-analysis of randomized placebo-controlled trials. Osteoarthritis and Cartilage/OARS. Osteoarthritis Research Society 2010;18(3):289–96. Epub 2009/10/28. http://dx.doi.org/10.1016/j.joca.2009.10.006. PubMed PMID: 19857509.
50. Citrome L, Weiss-Citrome A. A systematic review of duloxetine for osteoarthritic pain: what is the number needed to treat, number needed to harm, and likelihood to be helped or harmed? Postgrad Med 2012;124(1):83–93. Epub 2012/02/09. http://dx.doi.org/10.3810/pgm.2012.01.2521. PubMed PMID: 22314118.
51. Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlreich MM. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin 2011;27(12):2361–72. Epub 2011/10/25. http://dx.doi.org/10.1185/03007995.2011.633502. PubMed PMID: 22017192.
52. Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, *et al*. Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev 2005;(2):CD002946. Epub 2005/04/23. http://dx.doi.org/10.1002/14651858.CD002946.pub2. PubMed PMID: 15846645.
53. Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, *et al*. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. New Engl J Med 2006;354(8):795–808. Epub 2006/02/24. http://dx.doi.org/10.1056/NEJMoa052771. PubMed PMID: 16495392.
54. Palma Dos Reis R, Giacovelli G, Girolami F, Andre R, Bonazzi A, Rovati LC. Crystalline glucosamine sulfate in the treatment of osteoarthritis: evidence of long-term cardiovascular safety from clinical trials. Open Rheumatol J 2011;5:69–77. Epub 2012/01/05. http://dx.doi.org/10.2174/1874312901105010069. PubMed PMID: 22216067; PubMed Central PMCID: PMCPMC3245483.
55. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis–meta-analysis. Osteoarthritis and Cartilage/OARS. Osteoarthritis Research Society 2011;19(6):611–9. Epub 2011/03/30. http://dx.doi.org/10.1016/j.joca.2010.09.014. PubMed PMID: 21443958.
56. Rutjes AW, Juni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Intern Med 2012;157(3):180–91. Epub 2012/08/08. http://dx.doi.org/10.7326/0003-4819-157-3-201208070-00473. PubMed PMID: 22868835.
57. Lee C, Hunsche E, Balshaw R, Kong SX, Schnitzer TJ. Need for common internal controls when assessing the relative efficacy of pharmacologic agents using a meta-analytic approach: case study of cyclooxygenase 2-selective inhibitors for the treatment of osteoarthritis. Arthritis Rheum 2005;53(4):510–8. Epub 2005/08/06. http://dx.doi.org/10.1002/art.21328. PubMed PMID: 16082648.
58. Nuesch E, Rutjes AW, Husni E, Welch V, Juni P. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database Syst Rev 2009;(4):CD003115. Epub 2009/10/13. http://dx.doi.org/10.1002/14651858.CD003115.pub3. PubMed PMID: 19821302.
59. Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. Cochrane Database Syst Rev 2006;(3):CD005522. Epub 2006/07/21. http://dx.doi.org/10.1002/14651858.CD005522.pub2. PubMed PMID: 16856101.

60. Iwamoto J, Takeda T, Sato Y, Matsumoto H. Effects of risedronate on osteoarthritis of the knee. Yonsei Med J 2010;51(2):164–70. Epub 2010/03/02. http://dx.doi.org/10.3349/ymj.2010.51.2.164. PubMed PMID: 20191005; PubMed Central PMCID: PMCPMC2824859.
61. Christensen R, Bartels EM, Altman RD, Astrup A, Bliddal H. Does the hip powder of Rosa canina (rosehip) reduce pain in osteoarthritis patients?–a meta-analysis of randomized controlled trials. Osteoarthritis and Cartilage/OARS, Osteoarthritis Research Society 2008;16(9):965–72. Epub 2008/04/15. http://dx.doi.org/10.1016/j.joca.2008.03.001. PubMed PMID: 18407528.
62. European Medicines Agency. Recommendation to restrict the use of Protelos/Osseor (strontium ranelate) [press release].

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Clinical effects of lateral wedge arch support insoles in knee osteoarthritis

A prospective double-blind randomized study

Ru-Lan Hsieh (MD)[a,b,*], Wen-Chung Lee (MD, PhD)[c]

Abstract

We compared the short-term efficacy of rigid versus soft lateral wedge arch support (LWAS) insoles for patients with knee osteoarthritis (OA), as assessed using the International Classification of Functioning, Disability and Health (ICF) system, through a prospective, double-blind, randomized controlled trial.

Participants who fulfilled the combined radiographic and clinical criteria for knee OA, as defined by the American College of Rheumatology, were randomly prescribed 1 pair of rigid or soft LWAS insoles. Body functions and structures were evaluated according to Kellgren–Lawrence scores, the Foot Posture Index, Hospital Anxiety and Depression Scale scores, the pain–pressure threshold, postural stability, dynamic balance, and fall risk; activities and participation were assessed according to 10-m fast speed walking, stair climbing and chair rising times, and Chronic Pain Grade questionnaire responses; and knee OA-related health status was evaluated using the Knee Injury and Osteoarthritis Outcome Score (KOOS). Hospital Anxiety and Depression Scale scores, the pain–pressure threshold, physical activity, balance, Chronic Pain Grade questionnaire responses, and the KOOS were recorded before treatment and at 1-, 2-, and 3-month follow-ups.

We enrolled 90 participants, 70 women and 20 men, with mean ages of 60.6 ± 10.8 and 63.1 ± 10.8 years in the rigid and soft LWAS insole groups, respectively. Repeated-measures analysis of covariance revealed significant time × group effect improvements in pain ($P = 0.008$ for the KOOS), stair ascent time ($P = 0.003$), daily living function ($P = 0.003$ for the KOOS), sports and recreation function ($P = 0.012$ for the KOOS), and quality of life ($P = 0.021$ for the KOOS) in the soft LWAS insole group.

Patients with knee OA who used soft LWAS insoles for a short term showed more significant improvement than did those who used rigid LWAS insoles in pain, physical activity, daily living function, sports and recreation function, and quality of life, which belong to the body functions and structures and the activities and participation components in the ICF scheme.

Abbreviations: ANCOVA = analysis of covariance, CI = confidence intervals, ICF = International Classification of Functioning, Disability and Health, KOOS = Knee Injury and Osteoarthritis Outcome Score, LWAS = lateral wedge arch support, OA = osteoarthritis.

Keywords: effect, insoles, knee, osteoarthritis

1. Introduction

Osteoarthritis (OA) is the most common arthritic complaint among adults and a leading cause of chronic physical disability.[1] The prevalence of knee OA in the general population has ranged from 8.1% to 10% in previous studies.[2,3] Older women have a significantly higher prevalence of knee OA compared with older men.[4,5] Differences in endogenous sex hormones, body composition, knee structure and biomechanics, and psychosocial characteristics may play a role in the increased risk of knee OA in women.[6–8] Patients with knee OA experience pain, swelling, muscular atrophy, and restricted movement; these problems may negatively affect physical activity, causing difficulties in activities of daily living and reducing quality of life.[9]

The main treatment for knee OA entails controlling pain and avoiding potential complications of therapy.[10] OA is frequently associated with coronary artery disease, diabetes, obesity, and hypertension, and might be related to metabolic syndrome.[11] Patients with knee OA are likely to be older and may experience comorbidities; this patient group is at a relatively high risk of adverse gastrointestinal and cardiovascular effects of medication and polypharmacy.[12] Therefore, nonoperative treatments, such as shoe insoles, knee braces, and gait modification strategies, are commonly prescribed for patients with knee OA[13,14]; among them, insoles have become frequently used in recent years.[15–18]

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In Taiwan, 49.5% to 51% of rehabilitation services at physical medicine and rehabilitation clinics are provided for musculoskeletal and soft tissue diseases,[19,20] and knee OA accounts for 4.6%.[20]

The increased external knee adduction moment throughout the stance phase of patients with knee OA increases their medial knee joint loading during gait. Lateral wedges shift the center of pressure laterally, reducing the external knee adduction moment and knee adduction angular impulses, alleviating pain, and improving function in patients with knee OA.[21,22] However, patients with knee OA exhibit more pronated feet than do healthy people.[23] Therefore, lateral wedge insoles may aggravate pronation and the ankle invertor moment.[24,25] An increased invertor moment may further increase the demand on those muscles, thus causing fatigue after prolonged use of the insoles.[26] The purposes of adding arch support to lateral wedge insoles are reducing ankle eversion and diminishing the ankle invertor moment.[26]

Although Abdallah et al reported that using lateral wedge arch support (LWAS) insoles did not immediately reduce the knee adduction moment significantly in patients with knee OA,[26] Yeh et al and Nakajima et al have demonstrated the immediate reduction of the peak external knee adduction moment and knee pain.[25,27] Our recent study demonstrated that rigid LWAS insoles maintain the subtalar joint in a neutral position, thus providing immediate improvement in physical activity and medium-term reduction in pain and improvement in physical activity and function.[28] However, because of the lack of a control group, we could not exclude the possibility that the improvement was caused by the natural recovery process.

The International Classification of Functioning, Disability and Health (ICF) describes functional health conditions from a biopsychosocial perspective.[29] Functional health status is reflected by the dynamic interaction of ICF components including body functions and structures, activities, participation, and personal and environmental factors.[30] Clinical investigations of the efficacy of OA therapies should include body functions and structures (e.g., pain, depression, and balance), and activities and participation (e.g., physical activity, activities of daily living, functional performance, and knee OA-related health status).

According to our research, no study has compared the efficacy of rigid LWAS insoles with that of soft LWAS insoles by applying ICF components to evaluate patients wearing self-selected comfortable shoes. The present study compared the short-term clinical efficacy of the 2 types of insoles for patients with knee OA by using the ICF system in a randomized, double-blind design. We hypothesized that the short-term use of both types of LWAS insoles would improve scores in measures of body functions and structures as well as activities and participation.

2. Methods

This was a prospective, randomized, double-blind clinical study examining patients with knee OA. Participants with confirmed diagnoses of bilateral knee OA were recruited from the clinic of the Department of Physical Medicine and Rehabilitation at a teaching hospital in Taipei, Taiwan. All participants fulfilled the combined radiographic and clinical criteria for knee OA, as defined by the American College of Rheumatology.[31] Specifically, patients with Kellgren–Lawrence scores of 2 or higher in the medial compartment, based on anteroposterior radiographic views of both knees while bearing weight, were recruited for this study. The participants ranged in age from 40 to 85 years. We excluded patients with a self-reported history of malignancy, stroke, or knee implant operations and women who were pregnant or planned to become pregnant. The research was approved by the Institutional Review Board of Shin Kong Wu Ho-Su Memorial Hospital, and the study was performed in accordance with the World Medical Association Declaration of Helsinki. Informed consent was obtained from each participant. The trial was registered on ClinicalTrials.gov (registration number: NCT01765101; registration date: January 9, 2013) and conducted from January 2013 to December 2013.

2.1. Participant evaluation

Specific components of the ICF, namely, personal factors, body functions and structures (impairment), activities (limitations), and participation (restrictions), were evaluated as described herein.

2.2. Demographic data

Demographic data, namely, participant age, sex, education level, marital status, smoking and drinking habits, and comorbidities, were collected, and the body mass index was calculated.

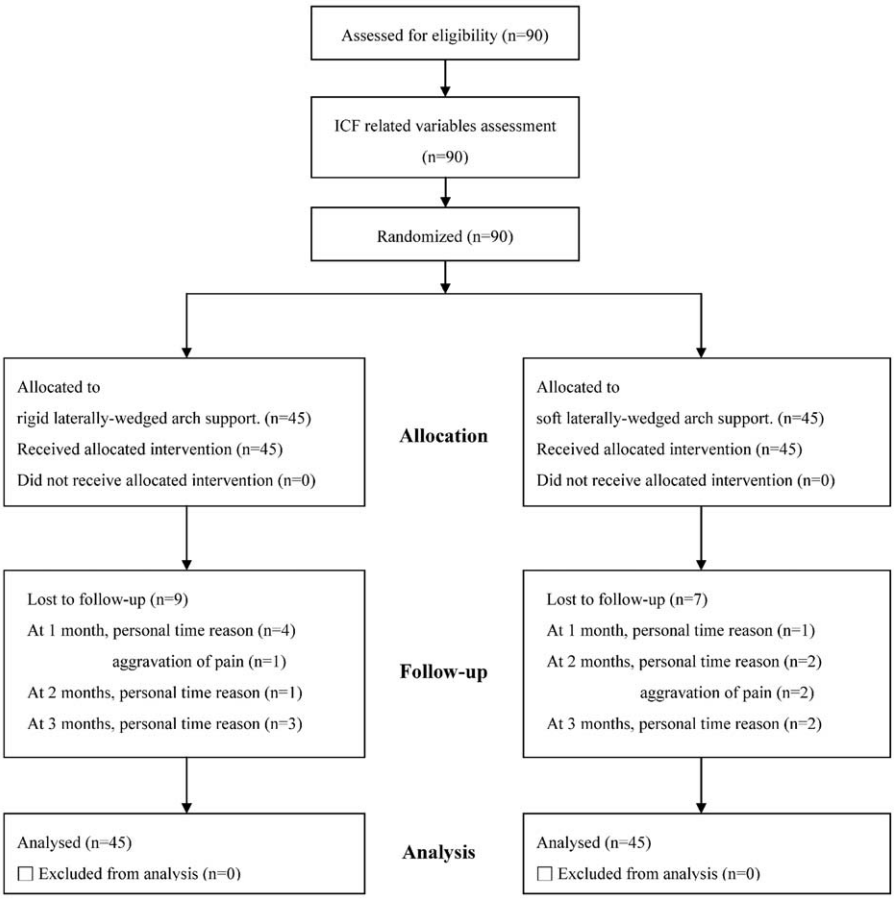
2.3. Body functions and structures

Foot posture was evaluated using the Foot Posture Index,[32] which is used to assess weight-bearing foot posture in a standing position according to a composite score of clinical observational criteria. Foot posture can be classified as follows: highly pronated (+10 to +12), pronated (+6 to +9), normal (0 to +5), supinated (−1 to −4), and highly supinated (−5 to −12). The index exhibited high intrarater reliability.[29]

Psychological distress was assessed using the Hospital Anxiety and Depression Scale.[33] Questions focused on feelings, states, and symptoms experienced during the preceding week. The scale comprises two 7-item subscales designed to measure anxiety and depression. A score exceeding 7 indicates the presence of anxiety and/or depression. The scale showed high reliability and validity.[34]

The pain–pressure threshold was measured using a pressure algometer, which was placed over the medial knee joint, 2 to 3 cm medial to the medial–lateral corner of the patella, with a contact area of 1 cm^2. Pressure was increased at a rate of 1 kg/s after force was vertically applied. The pain–pressure threshold was obtained by calculating the mean of 3 series of pain–pressure threshold assessments. The pain–pressure threshold was defined as the level of stimulation at which the participant first experiences a painful sensation.[25] The system exhibited high validity and reliability.[35]

Postural stability, dynamic balance, and fall risk were assessed using the Biodex Stability System,[36] which consists of an unstable platform for testing a patient's postural control and balance. The system can provide the degree of tilt of the platform along both the medial–lateral and anterior–posterior axes; thus, an overall stability index can be obtained. Higher scores indicate greater postural variability and less stability in balancing on the platform.[37] The Biodex Stability System evaluates dynamic balance by measuring limits of stability, which are recorded while the participants use their bodies to move a cursor on a monitor screen from a central box to peripheral boxes that appear randomly. Higher scores indicate greater control of dynamic balance.[38] The risk of falling was measured through 6 rounds of



Abbreviation: ICF, International of Functioning, Disability and Health.

Figure 1. Flow diagram. ICF = International Classification of Functioning, Disability and Health.

tests with varying levels of resistance. Higher scores indicate a greater risk of falling compared with those of sex- and age-matched normal controls.[38] The system has good inter-rater and intrarater reliability.[39,40] For safety, the participants adopted a bipedal stance on the platform, with their eyes open and feet bare. The feet positions were recorded to ensure the same stance throughout all future test sessions. Each participant was allowed 1 practice attempt, followed by 1 formal test for each assessment.

2.4. Activities and participation

Physical activity was measured through a 10-m walk test, a rising and sitting in a chair 5 times test, and a stair climb test. The tests were performed by asking participants to walk 10 m as fast as possible, to stand up and sit down on a standard chair 5 times without using their hands as quickly as possible, and to ascend and descend a flight of stairs (14 steps, and each step measured 18 cm in height) in the shortest time possible. The time taken to complete the tests was measured in seconds. A longer completion time indicates a greater limitation on physical activity.

The Chronic Pain Grade questionnaire containing 7 items was used to measure 3 subscales: pain intensity score, disability score, and disability point.[41] A higher score indicates greater symptoms and more severe disability. We used the disability score and disability point to assess for disability in the present study.

2.5. Knee OA-related health status

Participant perceptions of knee OA-related health status were assessed using the self-reported Knee Injury and Osteoarthritis Outcome Score (KOOS). A 5-point Likert scale was used to collect responses from the participants on 5 subscales: knee OA-related pain, other symptoms, daily living function, sports and recreation function, and knee-related quality of life.[42] Each scale ranges from 0 to 100, with 100 representing the least pain and dysfunction and 0 indicating the most pain and dysfunction. The system was reported to have high validity and reliability.[43]

2.6. Block randomization

After basic data were recorded and the aforementioned examinations were performed, the participants were allocated to either the rigid or the flexible LWAS insole group (Fig. 1). The principle of block randomization was used to assign the participants to the groups, with the block size being 4. Allocation was initially concealed. Sealed envelopes, 1 for each participant with the designated treatment group listed inside, were selected randomly when the participants were recruited for the study. One physician enrolled all participants, and another investigator generated the allocation sequence and assigned the participants to their groups.

Figure 2. Insole with a rigid lateral wedge and arch support.

2.7. Intervention

Each participant in the rigid LWAS insole group received a pair of thermoplastic insoles molded specifically for him or her by a qualified physiatrist. The insoles consisted of a 5° lateral wedge with an arch support composed of high-density ethyl vinyl acetate (ICB Medical, Australia), and the subtalar joint was maintained in a neutral position (Fig. 2). The procedure was detailed in a previous study.[28]

Each participant in the soft LWAS insole group received a pair of ready-made insoles consisting of a soft 5° lateral wedge and an arch support composed of polyurethane (Lanew, Taiwan) (Fig. 3).

All participants were blinded to the type of insole prescribed and all interventions were provided by the same physiatrist. Both groups were instructed to wear the insoles inside self-selected comfortable shoes for 1 hour on the first day and thereafter increase their usage by 1 hour per day until they wore the insoles whenever they wore shoes.

2.8. Follow-up assessment

An investigator blinded to group allocation evaluated ICF-related variables at 4 consecutive time points: before treatment and after the participants had worn the insoles for 1, 2, and 3 months. Both the participants and the investigator were blinded to the insole status during the treatment and data collection periods. The KOOS pain score was used as the primary outcome.

2.9. Sample size

To detect an effect size of 0.77 at an α level of 0.05 and power of 0.9, we had to evaluate at least 74 participants (37 participants for each group). Considering the possibility of 20% of the participants withdrawing during follow-up, we initially selected 90 participants (45 participants for each group).

2.10. Statistical analysis

The χ^2 or t test was used to analyze the data on demographics, body functions and structures, and activities and participation. The results are expressed as the mean ± standard deviation and 95% confidence intervals (CI). Repeated-measures analysis of covariance (ANCOVA) was used to assess the ICF-related variables (e.g., psychological distress, pain, balance, physical activity, disability, and knee OA-related health status) during follow-up assessments, with the baseline measurements used as covariates. The group effect, time effect, and group × time interaction effects for the 2 groups at the 3 postbaseline assessments were analyzed. The ANCOVA results are expressed as the F statistic, degrees of freedom, and P value. Intention-to-treat analysis (previous observation carried forward) was performed for all participants. The level of statistical significance was set at $P < 0.05$.

Figure 3. Insole with a soft lateral wedge and arch support.

3. Results

We enrolled 90 participants, 70 women and 20 men, with mean ages of 60.6 ± 10.8 and 63.1 ± 10.8 years in the rigid and soft LWAS insole groups, respectively. Table 1 presents the participants' demographic data. In the rigid LWAS insole group, 4 participants withdrew because of limited personal time, and 1 participant withdrew because of subjective aggravation of pain at the 1-month follow-up. Because of limited personal time, 1 and 3 participants withdrew at the 2- and 3-month follow-ups, respectively. In the soft LWAS insole group, 1 participant withdrew because of limited personal time at the 1-month follow-up. Two participants withdrew because of aggravation of pain and 2 participants withdrew because of limited personal time at the 2-month follow-up, and 2 participants withdrew because of limited personal time at the 3-month follow-up. Thus, a total of 74 participants completed the study (36 and 38 participants in the rigid and soft LWAS insole groups, respectively). The dropout rates were 20% and 15.6% in the rigid and soft LWAS insole groups, respectively. No significant differences were evident in the demographics of the participants who completed the study and those who withdrew (data not shown).

The scores in each outcome measure at each time point for each group and the mean differences between groups based on 95% CI are summarized in Tables 2 and 3. No significant differences were found between the groups in baseline scores for psychological distress (anxiety and depression), the pain–pressure threshold, postural stability and balance, physical activity (10-m fast speed walking, stair climbing, and chair rising times), disability severity, or the pain, symptoms, daily living function, sports and recreation function, and quality of life subscales of the KOOS. Table 2 lists the results of repeated-measures ANCOVA for the short-term effects of variables related to body functions and structures, and Table 3 presents the variables related to activities and participation. Compared with the results of baseline assessments, statistically significant group × time interaction improvements were noted in the soft LWAS group in pain ($P = 0.008$ for the KOOS), stair ascent time ($P = 0.003$), daily living function ($P = 0.003$ for the KOOS), sports and recreation function ($P = 0.012$ for the KOOS), and knee OA-related quality of life ($P = 0.021$ for the KOOS). Changes in the KOOS and stair ascent time of the 2 groups are shown in Fig. 4.

4. Discussion

This is the first study to apply the ICF system to patients with knee OA in a randomized, double-blind trial to compare the short-term clinical effects of wearing rigid and soft LWAS insoles. The use of soft LWAS insoles resulted in a significant short-term reduction in pain and improvements in stair ascent time, daily living function, sports and recreation function, and knee-related quality of life. The ICF system classifies these variables as belonging to the components of body functions and structures and activities and participation. In contrast to our assumption,

Table 1

Basic demographics of participants.

Variable	Rigid LWAS (n = 45)	Soft LWAS (n = 45)	*P*
Sex			0.379
Male	12 (26.7%)	8 (17.8%)	
Female	33 (73.3%)	37 (82.2%)	
Age	60.6 ± 10.8	63.1 ± 10.8	0.278
BMI, kg/m^2	25.1 ± 2.3	25.4 ± 3.1	0.583
Marriage			
Yes	35 (77.7%)	34 (75.6%)	0.371
Education			0.096
Below ninth grade	14	24	
Above ninth grade	31	21	
Comorbidities			
Yes	32 (74.4%)	30 (69.8%)	0.492
Smoking			
Yes	3 (6.7%)	2 (4.4%)	0.305
Drinking			
Yes	8 (17.7%)	8 (17.7%)	0.283
Foot Posture Index			
Left	6.93 ± 1.92	7.00 ± 1.57	0.323
Right	7.00 ± 1.90	7.00 ± 1.37	0.401
Kellgren–Lawrence score			
Left	2.40 ± 0.50	2.00 ± 0.49	0.500
Right	2.38 ± 0.49	2.00 ± 0.49	0.415

The scores are presented as the number of cases (percentage) or the mean ± standard deviation for each variable. BMI = body mass index, LWAS = lateral wedge arch support.

the short-term use of rigid LWAS insoles did not improve the scores of ICF-related items.

Patients with knee OA typically experience pain and psychological distress (e.g., anxiety and depression).[44] Pain associated with knee OA may interfere with the ability to perform activities of daily living.[44,45] Poor performance in activities of daily living and sports and recreation function may exacerbate the disabilities of patients and increase their economic burden.[46] Our previous study showed that patients with knee OA scored lower in postural stability and quality of life measures than did age-matched controls.[9] The present study demonstrated that the short-term use of soft LWAS insoles could alleviate pain and improve physical activity, daily living function, sports and recreation function, and knee-related quality of life in patients with knee OA.

During the midstance phase of normal gait, an estimated 60% to 75% of a person's body weight is distributed over the medial knee joint.[47] Patients with knee OA exhibit a greater knee adduction moment when walking than do age-matched controls.[48] Wedge insoles can realign the foot in either the varus or the valgus plane from 5° to 10°.[23] Lateral wedge insoles alleviate pain by reducing the external knee adduction moment[16] and diminishing the medial knee joint load.[15] Lateral wedge insoles also may activate muscles and change the spatial position of the lower limb,[15] can retard foot supination and accentuate foot pronation, and may aggravate pronation in an already overpronated ankle and foot.[23] Wedges might inhibit normal foot and ankle biomechanics, through mechanisms such as increasing the ankle invertor moment,[24] and thus exacerbate OA symptoms.[50]

Arch support insoles are commonly used clinically and improve foot alignment, shock attenuation, support, and stability during walking and running.[49,51,52] A 4% to 6% increase in the peak knee adduction moment during walking and running was observed in healthy young adults wearing arch support insoles.[51] However, no immediate change was reported in knee pain, the adduction moment, or the adduction angular moment with the use of arch support insoles in athletic shoes by patients with knee OA.[53] Differences in ages, populations (healthy adults vs. patients with knee OA), and types of shoes might have affected the results of these studies.

LWAS insoles reduce the peak knee external adduction moment in patients with knee OA by laterally shifting the center of pressure to reduce the frontal plane ground reaction force and lever arm.[26] They also change the step width, progression angle, and valgus angle at the subtalar joint, enabling users to walk more naturally.[28] Although arches added to lateral wedge insoles are aimed at reducing ankle eversion, wearing LWAS insoles did not reduce the ankle invertor moment to a normal level in 1 study.[26] Previous studies have revealed that a larger angle in a lateral wedge insole increases the unloading force at the knee joint, causing greater ankle and foot discomfort.[16,54] Therefore, in this study, we provided the participants with insoles with a 5° lateral wedge and arch support.

People generally prefer wearing different shoes at various times, depending on personal preference and comfort. There are numerous shoe types, such as soft, lightweight, conventional walking, stability, and athletic shoes.[55] We allowed the participants to wear self-selected comfortable shoes in the present study. Soft shoes have the biomechanical advantages of barefoot walking, such as the absence of a lifted heel and stiff soles, and thus effectively reduce knee joint loads in patients with knee OA.[55] Soft insoles might have the same benefits as do soft shoes, thereby improving physical activity and knee OA-related health status, including pain, daily living function, sports and recreation function, and quality of life. Additional studies examining various insole and shoe type combinations are recommended.

Although our research represents a reasonable initial foray into the effects of LWAS insoles in patients with knee OA, we acknowledge that many factors, such as the rigidity of insoles, whether insoles are custom molded or ready-made, height of the

Table 2

Body function scores.

	Rigid LWAS (n = 45)	Soft LWAS (n = 45)	Mean difference (95% CI)	*P*	*F* test	Group (*P*)	Time (*P*)	Group × time (*P*)
HADS								
Anxiety						0.076	0.354	0.327
T0	6.78 ± 3.95	7.73 ± 3.62	−0.95 (−2.57, 0.67)	0.247	$F(3, 24) = 1.4728$			
T1	6.05 ± 4.27	7.52 ± 3.87	−1.48 (−3.24, 0.29)	0.100	$F(3, 24) = 2.3274$			
T2	5.98 ± 3.64	7.86 ± 3.82	−1.88 (−3.51, −0.25)	0.024	$F(3, 24) = 3.7641$			
T3	6.84 ± 3.45	7.08 ± 3.25	−0.24 (−1.78, 1.30)	0.758	$F(3, 24) = 0.3946$			
Depression						0.153	0.617	0.658
T0	7.10 ± 2.92	8.00 ± 3.08	−0.90 (−2.21, 0.41)	0.174	$F(3, 24) = 1.8006$			
T1	6.90 ± 2.72	8.03 ± 2.73	−1.12 (−2.32, 0.08)	0.067	$F(3, 24) = 2.7176$			
T2	6.83 ± 3.00	7.86 ± 3.06	−1.03 (−2.35, 0.30)	0.127	$F(3, 24) = 2.0984$			
T3	7.08 ± 3.03	7.49 ± 3.17	−0.41 (−1.83, 1.02)	0.571	$F(3, 24) = 0.6832$			
Pain–pressure threshold								
Left						0.325	0.681	0.858
T0	2.55 ± 1.08	2.29 ± 1.06	0.26 (−0.19, 0.72)	0.252	$F(3, 24) = 1.4541$			
T1	2.18 ± 1.02	2.02 ± 0.76	0.16 (−0.22, 0.55)	0.410	$F(3, 24) = 0.9996$			
T2	2.35 ± 0.74	2.08 ± 0.84	0.27 (−0.08, 0.62)	0.123	$F(3, 24) = 2.1289$			
T3	2.54 ± 1.18	2.38 ± 1.05	0.16 (−0.36, 0.68)	0.548	$F(3, 24) = 0.7232$			
Right						0.939	0.748	0.753
T0	2.19 ± 1.07	2.28 ± 0.94	−0.09 (−0.51, 0.34)	0.682	$F(3, 24) = 0.5057$			
T1	2.38 ± 1.09	2.00 ± 0.81	0.38 (−0.03, 0.79)	0.072	$F(3, 24) = 2.6468$			
T2	2.14 ± 0.72	2.25 ± 0.82	−0.11 (−0.45, 0.23)	0.537	$F(3, 24) = 0.7429$			
T3	2.44 ± 1.10	2.26 ± 0.89	0.18 (−0.28, 0.64)	0.439	$F(3, 24) = 0.9352$			
Biodex Stability System								
Postural stability						0.097	0.996	0.712
T0	0.57 ± 0.25	0.75 ± 0.42	−0.18 (−0.33, −0.03)	0.015	$F(3, 24) = 4.2686$			
T1	0.73 ± 0.36	0.84 ± 0.51	−0.11 (−0.30, 0.08)	0.240	$F(3, 24) = 1.4996$			
T2	0.66 ± 0.30	0.92 ± 0.84	−0.26 (−0.54, 0.02)	0.069	$F(3, 24) = 2.6887$			
T3	0.63 ± 0.35	0.68 ± 0.40	−0.05 (−0.22, 0.13)	0.599	$F(3, 24) = 0.6362$			
Limits of stability						0.744	0.672	0.341
T0	45.69 ± 11.65	48.46 ± 10.82	−2.77 (−7.53, 2.00)	0.251	$F(3, 24) = 1.4578$			
T1	46.81 ± 13.24	47.91 ± 13.42	−1.10 (−6.82, 4.62)	0.703	$F(3, 24) = 0.4744$			
T2	45.25 ± 12.94	50.07 ± 13.86	−4.82 (−10.76, 1.11)	0.109	$F(3, 24) = 2.2445$			
T3	44.18 ± 13.97	49.97 ± 11.73	−5.79 (−11.78, 0.21)	0.058	$F(3, 24) = 2.8605$			
Fall risk						0.368	0.343	0.962
T0	2.45 ± 2.04	2.91 ± 1.53	−0.46 (−1.23, 0.30)	0.230	$F(3, 24) = 1.5393$			
T1	2.19 ± 1.76	2.35 ± 1.52	−0.16 (−0.86, 0.55)	0.653	$F(3, 24) = 0.5500$			
T2	1.90 ± 1.00	2.52 ± 1.75	−0.61 (−1.25, 0.02)	0.057	$F(3, 24) = 2.8778$			
T3	2.24 ± 1.65	2.62 ± 1.91	−0.38 (−1.21, 0.45)	0.363	$F(3, 24) = 1.1138$			
KOOS								
Pain						0.049*	<0.001†	0.008†
T0	40.94 ± 16.38	37.27 ± 17.27	3.67 (−3.55, 10.90)	0.315	$F(3, 24) = 1.2462$			
T1	41.10 ± 13.64	38.20 ± 15.77	2.91 (−3.43, 9.24)	0.364	$F(3, 24) = 1.1112$			
T2	42.89 ± 15.75	42.83 ± 14.91	0.06 (−6.68, 6.80)	0.987	$F(3, 24) = 0.0450$			
T3	41.55 ± 17.57	47.68 ± 14.42	−6.13 (−13.48, 1.22)	0.101	$F(3, 24) = 2.3178$			
Symptoms						0.900	0.265	0.343
T0	37.47 ± 16.83	39.35 ± 18.58	−1.88 (−9.49, 5.74)	0.625	$F(3, 24) = 0.5940$			
T1	35.74 ± 15.11	37.52 ± 16.47	−1.78 (−8.57, 5.01)	0.604	$F(3, 24) = 0.6280$			
T2	36.98 ± 17.18	39.26 ± 17.43	−2.28 (−9.89, 5.33)	0.553	$F(3, 24) = 0.7144$			
T3	36.23 ± 15.48	41.54 ± 15.05	−5.31 (−12.29, 1.67)	0.134	$F(3, 24) = 2.0474$			

Scores are expressed as the mean ± standard deviation. We report the *F* statistic from a repeated-measures ANCOVA as $F(df_{time}, df_{error}) = F$ test. ANCOVA = analysis of covariance, CI = confidence interval; HADS = Hospital Anxiety and Depression Scale, KOOS = Knee Injury and Osteoarthritis Outcome Score, LWAS = lateral wedge arch support, T0 = time point before treatment, T1 = time point after 1 month of treatment, T2 = time point after 2 months of treatment, T3 = time point after 3 months of treatment.

* $P < 0.05$.

† $P < 0.01$.

medial arch, angle of the lateral wedge, insole construction, usage duration, shoe type, and age factors, affect the results. Therefore, the long-term effects of different types of insoles in patients with knee OA require further investigation.

The main strength of this study was its use of reliable and patient-centered objective and subjective measurements based on the ICF model and recorded using a double-blind, randomized design. The ICF model provides clinicians with knowledge on specific components relevant to the observed therapeutic effects of the LWAS insoles.

This study was subject to several limitations. First, we did not evaluate the biomechanical effects of the insoles; this topic warrants

Table 3

Activities and participation of participants.

	Rigid LWAS (n = 45)	Soft LWAS (n = 45)	Mean difference (95% CI)	*P*	*F* test	Group (*P*)	Time (*P*)	Group × time (*P*)
Physical activity								
10-m fast walking						0.039*	0.003†	0.213
T0	8.36 ± 2.58	9.29 ± 2.96	−0.93 (−2.11, 0.25)	0.121	$F(3, 24) = 2.1446$			
T1	7.96 ± 1.73	8.76 ± 2.39	−0.80 (−1.70, 0.10)	0.078	$F(3, 24) = 2.5685$			
T2	7.97 ± 1.45	8.61 ± 2.12	−0.64 (−1.45, 0.16)	0.116	$F(3, 24) = 2.1849$			
T3	8.03 ± 1.43	8.39 ± 2.22	−0.36 (−1.21, 0.50)	0.408	$F(3, 24) = 1.0042$			
Stair ascent time						<0.001†	<0.001†	0.003†
T0	11.07 ± 2.60	14.56 ± 7.43	−3.49 (−5.89, −1.09)	0.004	$F(3, 24) = 5.7861$			
T1	10.77 ± 2.83	13.14 ± 5.04	−2.37 (−4.16, −0.59)	0.009	$F(3, 24) = 4.8371$			
T2	10.80 ± 2.54	12.44 ± 4.24	−1.64 (−3.19, −0.09)	0.037	$F(3, 24) = 3.3141$			
T3	10.76 ± 3.30	11.65 ± 4.25	−0.89 (−2.63, 0.85)	0.373	$F(3, 24) = 1.0884$			
Stair descent time						0.003†	0.001†	0.058
T0	10.69 ± 3.51	13.60 ± 6.14	−2.91 (−5.06, −0.77)	0.007	$F(3, 24) = 5.1249$			
T1	10.20 ± 3.15	12.36 ± 5.40	−2.16 (−4.08, −0.23)	0.026	$F(3, 24) = 3.6799$			
T2	10.28 ± 3.22	12.54 ± 5.81	−2.27 (−4.35, −0.18)	0.033	$F(3, 24) = 3.3417$			
T3	10.16 ± 3.00	10.95 ± 4.07	−0.79 (−2.42, −0.85)	0.341	$F(3, 24) = 1.1722$			
Chair rising time						0.278	<0.001†	0.954
T0	16.39 ± 4.86	17.73 ± 6.18	−1.34 (−3.72, 1.03)	0.263	$F(3, 24) = 1.4143$			
T1	15.58 ± 4.95	17.03 ± 5.70	−1.45 (−3.75, 0.84)	0.211	$F(3, 24) = 1.6199$			
T2	15.34 ± 4.32	16.18 ± 5.13	−0.84 (−2.95, 1.26)	0.426	$F(3, 24) = 0.9636$			
T3	14.36 ± 3.65	15.55 ± 6.42	−1.19 (−3.58, 1.21)	0.326	$F(3, 24) = 1.2142$			
Chronic Pain Grade questionnaire								
Disability score						0.576	0.089	0.879
T0	38.65 ± 21.75	40.59 ± 24.60	−1.94 (−11.87, 7.99)	0.698	$F(3, 24) = 0.4818$			
T1	33.82 ± 21.57	38.94 ± 23.15	−5.12 (−14.79, 4.55)	0.296	$F(3, 24) = 1.3042$			
T2	35.58 ± 20.64	40.41 ± 22.68	−4.82 (−14.42, 4.77)	0.320	$F(3, 24) = 1.2315$			
T3	29.72 ± 16.72	32.11 ± 23.11	−2.38 (−11.78, 7.01)	0.615	$F(3, 24) = 0.6101$			
Disability points						0.465	0.117	0.817
T0	3.91 ± 2.35	4.13 ± 2.56	−0.22 (−1.26, 0.82)	0.687	$F(3, 24) = 0.4982$			
T1	3.38 ± 2.23	4.30 ± 2.26	−0.91 (−1.87, 0.03)	0.075	$F(3, 24) = 2.6068$			
T2	3.44 ± 2.08	4.22 ± 2.34	−0.78 (−1.71, 0.15)	0.134	$F(3, 24) = 2.0474$			
T3	2.98 ± 1.76	3.38 ± 2.30	−0.40 (−1.26, 0.46)	0.436	$F(3, 24) = 0.9417$			
KOOS								
Daily living function						0.007†	<0.001†	0.003†
T0	45.01 ± 14.20	38.01 ± 17.00	7.01 (0.31, 13.71)	0.041	$F(3, 24) = 3.2093$			
T1	44.54 ± 14.06	40.85 ± 14.34	3.70 (−2.40, 9.79)	0.231	$F(3, 24) = 1.5353$			
T2	47.47 ± 16.24	44.56 ± 14.27	2.90 (−3.82, 9.62)	0.393	$F(3, 24) = 1.0394$			
T3	44.80 ± 16.30	47.99 ± 14.44	−3.19 (−10.28, 3.91)	0.374	$F(3, 24) = 1.0859$			
Sports and recreation function						0.033	<0.001†	0.012*
T0	21.22 ± 26.87	14.03 ± 23.63	7.19 (−3.64, 18.02)	0.190	$F(3, 24) = 1.7180$			
T1	23.72 ± 25.11	16.09 ± 22.31	7.64 (−2.61, 17.88)	0.142	$F(3, 24) = 1.9924$			
T2	21.56 ± 22.47	26.18 ± 21.89	−4.62 (−14.43, 5.19)	0.352	$F(3, 24) = 1.1426$			
T3	23.07 ± 23.73	27.84 ± 20.77	−4.77 (−15.04, 5.51)	0.358	$F(3, 24) = 1.1268$			
Quality of life						0.266	<0.001†	0.021*
T0	19.92 ± 19.22	19.12 ± 18.45	0.80 −7.28, 8.88)	0.845	$F(3, 24) = 0.2719$			
T1	22.37 ± 22.47	20.22 ± 19.87	2.15 (−6.93, 11.24)	0.639	$F(3, 24) = 0.5718$			
T2	21.61 ± 22.07	26.47 ± 18.90	−4.86 (−13.94, 4.22)	0.290	$F(3, 24) = 1.3233$			
T3	24.62 ± 20.89	32.60 ± 17.65	−7.99 (−16.90, 0.93)	0.078	$F(3, 24) = 2.5685$			

Scores are expressed as the mean ± standard deviation. We report the *F* statistic from a repeated-measures ANCOVA as $F(df_{time}, df_{error}) = F$ test. ANCOVA = analysis of covariance, CI = confidence interval, KOOS = Knee Injury and Osteoarthritis Outcome Score, LWAS = lateral wedge arch support, T0 = time point before treatment, T1 = time point after 1 month of treatment, T2 = time point after 2 months of treatment, T3 = time point after 3 months of treatment

* $P < 0.05$.

† $P < 0.01$.

further investigation. Second, we followed the participants for only 3 months; whether the observed short-term benefits of the soft LWAS insoles continue after prolonged use is unclear. Third, factors such as insole construction, arch support height, lateral wedge angle, and shoe type might affect the study results. Long-term follow-up studies comparing different types of insoles and shoes are warranted. Finally, the total number of patients (90) was not high, with 78% being women, and 17.8% of dropout rate. Therefore, our study provides only preliminary but valuable data that should be validated in a larger study. Future studies should have a larger sample size and use a community-based sample to confirm the generalizability of our results.

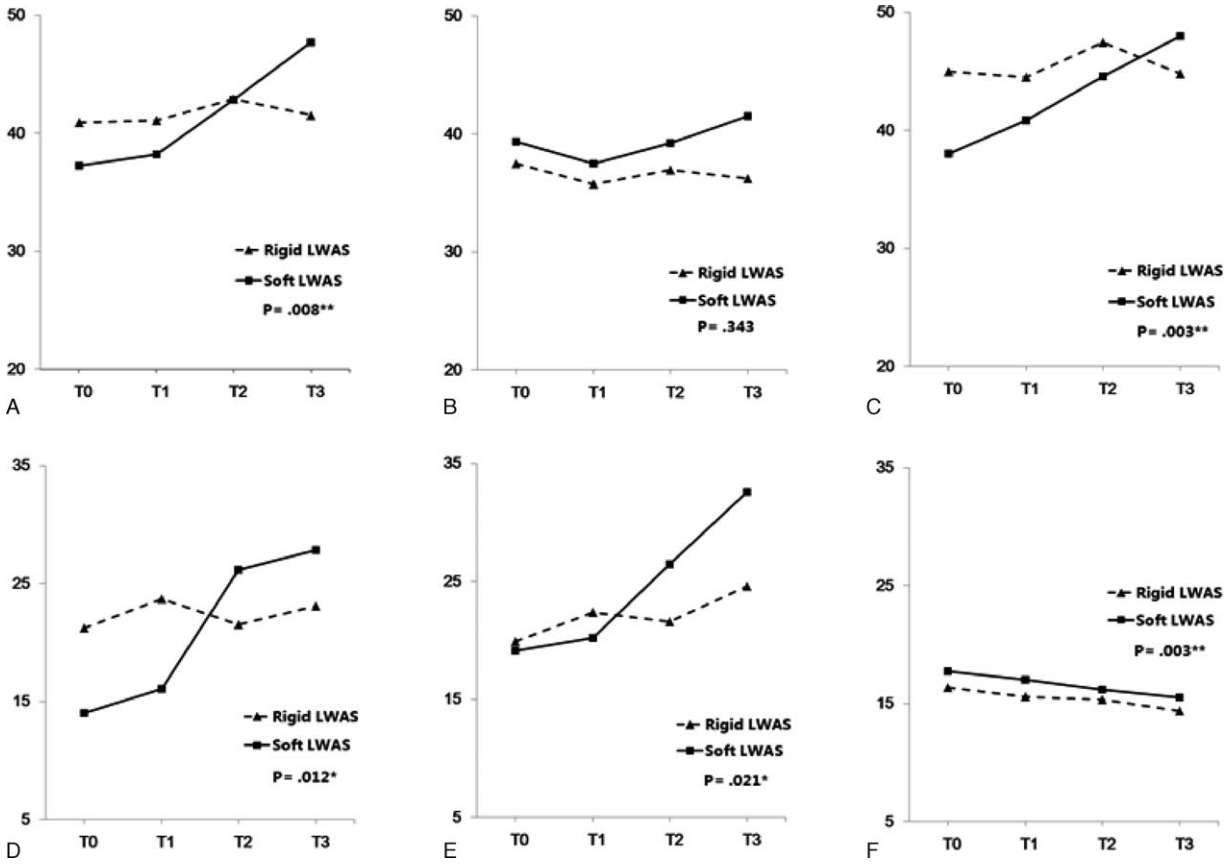


Figure 4. Changes in KOOS and stair ascent time. Triangles and squares represent the rigid and flexible LWAS insole groups, respectively. (A) KOOS pain subscale; (B) KOOS other symptoms subscale; (C) KOOS daily living function subscale; (D) KOOS sports and recreation function subscale; (E) KOOS knee-related quality of life subscale; and (F) stair ascent time. KOOS = Knee Injury and Osteoarthritis Outcome Score, LWAS = lateral wedge arch support, T0 = time point before treatment, T1 = time point after 1 month of treatment, T2 = time point after 2 months of treatment, T3 = time point after 3 months of treatment. Group × time interaction effects: (*) $P < 0.05$; (**) $P < 0.01$.

5. Conclusions

Patients with knee OA who received short-term therapy with soft LWAS insoles experienced significant pain alleviation and improvements in physical activity, daily living function, sports and recreation function, and quality of life. These variables are classified in the body functions and structures and the activities and participation components in the ICF scheme. Additional clinical trials evaluating the biomechanical effects and the long-term efficacy of different types of insoles in patients with knee OA are necessary.

References

[1] Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 disease and injuries 1990–2010: a systematic analysis for the Global Burden of Diseases Study 2010. Lancet 2012;380:2163–96.

[2] Tang X, Wang S, Zhan S, et al. The prevalence of symptomatic knee osteoarthritis in China: results from the China Health and Retirement Longitudinal Study. Arthritis Rheumatol 2016;68:648–53.

[3] Hiligsmann M, Cooper C, Arden N, et al. Health economics in the field of osteoarthritis: an expert's consensus paper from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Semin Arthritis Rheum 2013;43:303–13.

[4] Woo J, Leung J, Lau E. Prevalence and correlates of musculoskeletal pain in Chinese elderly and the impact on 4-year physical function and quality of life. Public Health 2009;123:549–56.

[5] Srikanth VK, Fryer JL, Zhai G, et al. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthritis Cartilage 2005;13:769–81.

[6] Glass N, Segal NA, Sluka KA, et al. Examining sex differences in knee pain: the multicenter osteoarthritis study. Osteoarthritis Cartilage 2014;22:1100–6.

[7] Smith SL, Woodburn J, Steultjens MP. Electromechanical delay and rate of force development in individuals with knee osteoarthritis. Osteoarthritis Cartilage 2016;24:S122.

[8] Jin X, Wang B, Wang X, et al. Associations between endogenous sex hormones and MRI structural changes in patients with symptomatic knee osteoarthritis. Osteoarthritis Cartilage 2016;24:S358–9.

[9] Hsieh RL, Lee WC, Lo MT, et al. Postural stability in patients with knee osteoarthritis: comparison with controls and evaluation of relationships between International Classification of Functioning, Disability, and Health. Arch Phys Med Rehabil 2013;94:340–6.

[10] Felson DT, Lawrence RC, Hochberg MC, et al. Osteoarthritis: new insights. Part 2: treatment approaches. Ann Intern Med 2000;133:726–37.

[11] Sellam J, Berenbaum F. Is osteoarthritis a metabolic disease? Joint Bone Spine 2013;80:568–73. 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;64:465–74.

[12] Simic M, Wrigley TV, Hinman RS, et al. Altering foot progression angle in people with medial knee osteoarthritis: the effects of varying toe-in and toe-out angles are mediated by pain and malalignment. Osteoarthritis Cartilage 2013;21:1272–80.

[13] Raja K, Dewan N. Efficacy of knee braces and foot orthoses in conservative management of knee osteoarthritis: a systematic review. Am J Phys Med Rehabil 2011;90:247–62.

[14] Yasuda K, Sasaki T. The mechanics of treatment of the osteoarthritic knee with a wedged insole. Clin Orthop Relat Res 1987;215:162–72.
[15] Kerrigan DC, Lelas JL, Goggins J, et al. Effectiveness of a lateral-wedge insole on knee varus torque in patients with knee osteoarthritis. Arch Phys Med Rehabil 2002;83:889–93.
[16] Hinman RS, Bennell KL. Advances in insoles and shoes for knee osteoarthritis. Curr Opin Rheumatol 2009;21:164–70.
[17] Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008;16:137–62.
[18] Hinman RS, Bowles KA, Metcalf BB, et al. Lateral wedge insoles for medial knee osteoarthritis: effects on lower limb frontal plane biomechanics. Clin Biomech 2012;27:27–33.
[19] Hsieh RL, Lein IN, Hsieh LF, et al. Study on disease classification of rehabilitation patients in eight hospitals at northern and western Taiwan. J Rehabil Med Assoc 1996;24:35–40.
[20] Chung-Po S, Ssu-Yuan C, Tyng-Guey W, et al. Primary reasons for rehabilitation service referrals: the recent experience of a medical center in Taiwan. Taiwan J Phys Med Rehabil 2010;38:229–36.
[21] Jones RK, Nester CJ, Richards JD, et al. A comparison of the biomechanical effects of valgus knee braces and lateral wedged insoles in patients with knee osteoarthritis. Gait Posture 2013;37:368–72.
[22] Levinger P, Menz HB, Fotoohabadi MR, et al. Foot posture in people with medial compartment knee osteoarthritis. J Foot Ankle Res 2010;3:29.
[23] Baker K, Goggins J, Xie H, et al. A randomized crossover trial of a wedged insole for treatment of knee osteoarthritis. Arthritis Rheum 2007;56:1198–203.
[24] Butler RJ, Barrios JA, Royer T, et al. Effect of laterally wedged foot orthoses on rearfoot and hip mechanics in patients with medial knee osteoarthritis. Prosthet Orthot Int 2009;33:107–16.
[25] Yeh HC, Chen LF, Hsu WC, et al. Immediate efficacy of laterally wedged insoles with arch support on walking in persons with bilateral medial knee osteoarthritis. Arch Phys Med Rehabil 2014;95:2420–7.
[26] Abdallah AA, Radwan AY. Biomechanical changes accompanying unilateral and bilateral use of laterally wedged insoles with medial arch supports in patients with medial knee osteoarthritis. Clin Biomech (Bristol, Avon) 2011;26:783–9.
[27] Nakajima K, Kakihana W, Nakagawa T, et al. Addition of an arch support improves the biomechanical effect of a laterally wedged insole. Gait Posture 2009;29:208–13.
[28] Hsieh RL, Lee WC. Immediate and medium-term effects of custom-moulded insoles on pain, physical function, physical activity, and balance control in patients with knee osteoarthritis. J Rehabil Med 2014;46:159–65.
[29] WHO. *International Classification of Functioning, Disability and Health (ICF)*. Geneva, Switzerland: World Health Organization; 2001.
[30] Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039–49.
[31] Redmond AC, Crosbie J, Ouvrier RA. Development and validation of a novel rating system for scoring standing foot posture: the Foot Posture Index. Clin Biomech 2006;21:89–98.
[32] Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67:361–70.
[33] Bjelland I, Dahl AA, Haug TT, et al. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 2002;52:69–77.
[34] Abrishami A, Chan J, Chung F, et al. Preoperative pain sensitivity and its correlation with postoperative pain and analgesic consumption: a qualitative systematic review. Anesthesiology 2011;114:445–57.
[35] Kinser AM, Sands WA, Stone MH. Reliability and validity of a pressure algometer. J Strength Cond Res 2009;23:312–4.
[36] BiodexBiodex Balance System: Clinical Resource Manual. Shirley: Biodex Medical System, Inc; 1999.
[37] Pien LC, Chu H, Chen WC, et al. Reliability and validity of a Chinese version of the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF-C). J Clin Nurs 2011;20:2224–32.
[38] Tseng WC, Hsieh RL. Effects of short-term active video game play on community adults: under International Classification of Functioning, Disability and Health consideration. Chin Med J (Engl) 2013;126:2313–9.
[39] Schmitz R, Arnold B. Intertester and intratester reliability of a dynamic balance protocol using the Biodex Stability System. J Sport Rehabil 1998;7:95–101.
[40] Cachupe WJC, Shifflett B, Kahanov L, et al. Reliability of Biodex balance system measures. Meas Phys Educ Exerc Sci 2001;5:97–108.
[41] Smith BH, Penny KI, Purves AM, et al. The Chronic Pain Grade questionnaire: validation and reliability in postal research. Pain 1997;71:141–7.
[42] Roos EM, Lohmander LS. The Knee Injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes 2003;1:64.
[43] Xie F, Li SC, Roos EM, et al. Cross-cultural adaptation and validation of Singapore English and Chinese versions of the Knee Injury and Osteoarthritis Outcome Score (KOOS) in Asians with knee osteoarthritis in Singapore. Osteoarthritis Cartilage 2006;14:1098–103.
[44] Somers TJ, Keefe FJ, Godiwala N, et al. Psychosocial factors and the pain experience of osteoarthritis patients: new findings and new directions. Curr Opin Rheumatol 2009;21:501–6.
[45] Dekker J, van Dijk GM, Veenhof C. Risk factors for functional decline in osteoarthritis of the hip or knee. Curr Opin Rheumatol 2009;21:520–4.
[46] Danter JH. Alleviating the pain of arthralgias. Nurse Pract 2009;34:40–6.
[47] Krohn K. Footwear alterations and bracing as treatments for knee osteoarthritis. Curr Opin Rheumatol 2005;17:653–6.
[48] Hurwitz D, Ryals A, Case J, et al. The knee adduction moment during gait in subjects with knee osteoarthritis is more closely correlated with static alignment than radiographic disease severity, toe out angle and pain. J Orthop Res 2002;20:101–7.
[49] Iorio R, Healy WL. Unicompartmental arthritis of the knee. J Bone Joint Surg Am 2003;85-A:1351–64.
[50] Yonclas PP, Nadler RR, Moran ME, et al. Orthotics and assistive devices in the treatment of upper and lower limb osteoarthritis: an update. Am J Phys Med Rehabil 2006;85:S82–97.
[51] Franz JR, Dicharry J, Riley PO, et al. The influence of arch supports on knee torques relevant to knee osteoarthritis. Med Sci Sports Exerc 2008;40:913–7.
[52] Windle CM, Gregory SM, Dixon SJ. The shock attenuation characteristics of four different insoles when worn in a military boot during running and marching. Gait Posture 1999;9:31–7.
[53] Hinman RS, Bardin L, Simic M, et al. Medial arch supports do not significantly alter the knee adduction moment in people with knee osteoarthritis. Osteoarthritis Cartilage 2013;21:28–34.
[54] Shelburne KB, Torry MR, Steadman JR, et al. Effects of foot orthoses and valgus bracing on the knee adduction moment and medial joint load during gait. Clin Biomech (Bristol, Avon) 2008;23:814–21.
[55] Shakoor N, Lidtke RH, Sengupta M, et al. Effects of specialized footwear on joint loads in osteoarthritis of the knee. Arthritis Rheum 2008;59:1214–20.

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Physical Activity and Exercise Therapy Benefit More Than Just Symptoms and Impairments in People With Hip and Knee Osteoarthritis

Osteoarthritis (OA) is among the leading causes of global disability, with the hip and knee contributing most to the burden.[20] Knee OA alone is estimated to affect approximately 250 million people worldwide.[88] Importantly, most people with OA are of working age, with more than half being younger than 65 years of age,[24] and the prevalence of OA is expected to continue its dramatic increase in the future.[20] Furthermore, OA is a significant barrier to physical activity, due to activity-related pain associated with the disease.[25] Physical inactivity is an underappreciated causal factor of most chronic diseases, including OA, type 2 diabetes, cardiovascular disease (CVD), some types of cancer, and dementia.[17] Therefore, an evidence-based approach is greatly needed to address the future burden and associated costs of not only symptoms and impairments in OA, but also physical inactivity.

SYNOPSIS: Osteoarthritis (OA) of the hip and knee is among the leading causes of global disability, highlighting the need for early, targeted, and effective treatment. The benefits of exercise therapy in people with hip and knee OA are substantial and supported by high-quality evidence, underlining that it should be part of first-line treatment in clinical practice. Furthermore, unlike other treatments for OA, such as analgesia and surgery, exercise therapy is not associated with risk of serious harm. Helping people with OA become more physically active, along with structured exercise therapy targeting symptoms and impairments, is crucial, considering that the majority of people with hip and knee OA do not meet physical activity recommendations. Osteoarthritis is associated with a range of chronic comorbidities, including type 2 diabetes, cardiovascular disease, and dementia, all of which are associated with chronic low-grade inflammation. Physical activity and exercise therapy not only improve symptoms and impairments of OA, but are also effective in preventing at least 35 chronic conditions and treating at least 26 chronic conditions, with one of the potential working mechanisms being exercise-induced anti-inflammatory effects. Patient education may be crucial to ensure long-term adherence and sustained positive effects on symptoms, impairments, physical activity levels, and comorbidities. *J Orthop Sports Phys Ther 2018;48(6):439-447. Epub 18 Apr 2018. doi:10.2519/jospt.2018.7877*

KEY WORDS: *comorbidity, implementation, nonsurgical treatment, osteoarthritis, patient education*

We Have a Solution: It's Not a Tablet, Injection, or Surgery

Exercise therapy is a safe and effective solution for managing both OA and a range of other chronic conditions that does not require potentially harmful and costly pharmacotherapy, injections, or surgery. Substantial evidence supports the effects of exercise therapy in the treatment of at least 26 chronic conditions,[64] including hip and knee OA.[33,34]

This clinical commentary presents the evidence for exercise therapy as an effective treatment for OA and suggests broad guidance on how to apply this evi-

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dence in clinical practice. Subsequently, it highlights the importance of promoting physical activity alongside structured exercise therapy and presents other health benefits that individuals with OA may experience from adequately designed and implemented exercise therapy programs. Finally, it discusses the importance of patient education to long-term adherence and benefits.

Exercise Therapy in OA

Exercise therapy is a specific type of physical activity designed and prescribed for specific therapeutic goals.[59] Compelling evidence from more than 50 randomized controlled trials (RCTs) in knee OA[33] and 10 RCTs in hip OA[34] supports the efficacy of land-based exercise therapy in reducing symptoms and impairments. Compared to the 2 most common pharmacological pain relievers, exercise therapy seems to be at least as effective as nonsteroidal anti-inflammatory drugs[8,33] and 2 to 3 times more effective than acetaminophen (paracetamol) in reducing pain in knee OA.[8] Like analgesic medication, exercise therapy needs to be taken at a sufficient dose and duration to be effective and ensure optimal and clinically relevant effects on symptoms and impairments (see the **TABLE** for key exercise therapy recommendations). Importantly, the pain-relieving effect of exercise therapy and other nonsurgical treatments is similar, regardless of knee OA severity, as evaluated by radiography[48,75] and pain intensity at baseline.[48] However, exercise therapy[66] is not associated with the same risk of adverse events as nonsteroidal anti-inflammatory drugs and acetaminophen.[8]

A range of different exercise programs have been used in RCTs of land-based exercise therapy for individuals with hip and knee OA.[33,34] When grouped into 3 broad categories that include aerobic (with the focus of improving cardiorespiratory fitness), resistance (with the focus of improving muscle strength), and performance (with the focus of improving the ability to perform specific activities) exercise, no significant differences in effects between types of exercise therapy could be identified.[48] Specifically, effect sizes (standardized mean difference) related to symptoms and impairments reported for aerobic (0.56-0.67), resistance (0.60-0.62), and performance (0.48-0.56) exercise therapy programs in people with knee OA are similar.[48] Based on this, some people might conclude that the choice of exercise therapy type is not important when treating symptoms and impairments in people with OA. However, several studies have identified subgroups of people with knee OA who benefit more from one type of exercise therapy than another[14,50,54]; for example, people with a visually observable varus thrust seem to benefit more from neuromuscular exercise than from quadriceps-strengthening exercise, while people who are obese seem to benefit more from quadriceps-strengthening exercise.[14] Therefore, there is potential to optimize treatment effects by choosing the most relevant exercise therapy type for the individual, based on his or her specific symptoms and impairments and values, circumstances, and needs. Although the benefits for symptoms and impairments from aquatic exercise therapy in the treatment of hip and knee OA are smaller than the effects from land-based exercise therapy,[9] aquatic exercise therapy may also be relevant for individuals with too much pain to exercise in a full–weight-bearing environment.

Previous research suggests that people with knee (and hip) OA have deficits in proprioceptive acuity, muscle strength, and ability to stabilize the joint.[16,18] It seems likely that both resistance exercise therapy targeting lower-limb strength and performance-based exercise therapy could help improve these deficits. Neuromuscular exercise is a specific type of exercise therapy often used to address these deficits and is reported to be effective without serious adverse effects in people with mild to severe hip and knee OA.[3,4,77,79,85] Neuromuscular exercises may be performed on both the symptomatic and asymptomatic legs and progressed or regressed based on the therapist's assessment of movement quality and control, and on the patient's report of pain and movement control.[3] Pain during exercise is allowable, as long as the individual finds it to be of an acceptable level, and any increase to normal pain and symptoms following the exercise session has reduced to the same level or lower within 24 hours (**FIGURE 1**).[3] Video examples of neuromuscular exercises can be found online at http://nemex.trekeducation.org/.[3] The exercises focus on the alignment of the weight-bearing leg, with the purpose of

TABLE Seven Exercise Therapy Recommendations for Hip and Knee Osteoarthritis

Recommendation	Description
1	Provide aerobic, resistance, performance, or neuromuscular exercises tailored and targeted to individual patient needs and preferences
2	Consider aquatic exercise in patients who are unable to adequately complete land-based exercise due to pain
3	Provide a minimum of 12 supervised exercise sessions of 30 to 60 minutes per session over a 6-week period (ie, 2 sessions per week)
4	Encourage an additional 1 to 2 sessions per week to optimize outcomes, particularly related to strength
5	Consider extending initial exercise therapy programs to 12 weeks or longer to optimize outcomes, particularly related to strength
6	Include patient education and consider booster sessions in the long term to enhance adherence and progression
7	Provide education and reassurance about managing potential pain flares and inflammation, and how to modify exercises and physical activity to ensure continued participation

moving the other leg to challenge stability and control.

It is clear from clinical trials evaluating the efficacy of exercise therapy for OA that not everyone achieves reduced symptoms and impairments from the same exercise prescription, and it is possible that some people with OA may not respond favorably to exercise prescription at all. However, considering the multiple forms of exercise therapy that might be effective (aerobic, resistance, and performance),[48] the treating therapist is encouraged to adapt the exercise prescription should people not respond favorably initially, and to ensure that people are educated about the various exercise options to try before abandoning an active approach to management of symptoms and impairments.

Total Number of Sessions and Supervision

Supervision of exercise therapy sessions may be particularly important for a variety of reasons. It allows the therapist an opportunity to adjust the level and type of exercise based on individual response (ie, perceived exertion and pain responses) and performance quality. Additionally, education on expectations regarding pain during exercises and other activities and reassurance about exercise performance can be provided, potentially enhancing self-efficacy. Current evidence suggests that a greater number of supervised exercise sessions, at least for aerobic exercise, may enhance the effects of exercise therapy in knee OA.[48] Specifically, more than 12 supervised exercise sessions appear to reduce symptoms and impairments to a greater extent than fewer than 12 sessions.[48] A recent systematic review and meta-analysis of supervised land-based exercise therapy for people with hip OA did not replicate that finding, potentially owing to insufficient reporting of the exercise dose in several of the included studies.[58] Although still unidentified, an upper limit of the number of exercise sessions where no further improvements can be expected does presumably exist. Regardless, the added benefits of greater volume of exercise therapy participation in both hip and knee OA to other systems in the body discussed below should also be considered.

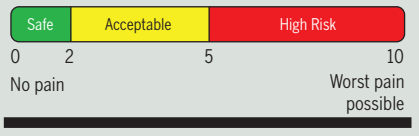

FIGURE 1. Visual analog scale that can be used to supervise pain during and after exercise therapy. Pain flares are acceptable as long as the pain intensity subsides to its baseline level within 24 hours. Acceptable pain is defined by the individual, but this proposed visual analog scale has been previously demonstrated to be feasible and relevant in people with hip and knee osteoarthritis.[3,76] Modified from Thomeé.[83]

A limitation related to previous trials evaluating exercise therapy for individuals with hip and knee OA is that it may be of insufficient duration to address common deficits, such as reduced hip and knee strength. Importantly, a recent systematic review and meta-regression indicates that an increase in knee extensor strength of less than 30% is not likely to lead to clinically meaningful improvements in symptoms and impairments for people with knee OA.[10] Considering that the majority of previous exercise therapy trials performed with individuals with knee OA are in the range of 4 to 12 weeks, with few exceeding 12 weeks, this magnitude of improvement is not likely to occur for programs of shorter duration. In practice, we recommend continuing exercise therapy well beyond 12 weeks when the aim is to address strength deficits and muscle atrophy resulting from the OA process.[36] Accordingly, booster sessions, where the individual revisits the therapist after the initial supervised exercise program has ended, seem to be relevant to improve long-term adherence,[1,65] although the evidence in support of this approach is not conclusive.[15,32]

Frequency, Duration, and Intensity of Exercise Therapy Sessions

Three or more exercise therapy sessions per week are more effective at addressing symptoms and impairments in individuals with hip and knee OA when compared to fewer than 2 sessions per week.[48] However, with an eye to feasibility in clinical practice, and referring to general recommendations for exercise among older people and people with chronic diseases,[31] 2 sessions per week of 30 to 60 minutes in duration, with the potential of 1 to 2 further sessions per week of unsupervised home exercise, could be a good starting point for people with hip and knee OA, especially for those with less experience in exercising.[2] Importantly, based on currently accepted exercise prescription recommendations from the American College of Sports Medicine, 2 sessions per week, with 2 to 4 sets of 8 to 12 repetitions at an intensity of 60% to 80% of the individual's 1-repetition maximum effort in a number of carefully selected exercises, are likely to address strength deficits seen in hip and knee OA.[36] In fact, supervised land-based exercise therapy interventions for people with hip OA with high compliance to the American College of Sports Medicine recommendations[36] resulted in greater improvements in symptoms and impairments compared to interventions with uncertain compliance.[58] Additionally, based on the nationwide implementation initiative Good Life with osteoArthritis in Denmark (GLA:D), implementing education and 2 sessions of supervised neuromuscular exercise therapy per week for 6 weeks leads to a significant positive impact on patient symptoms, impairments, consumption of pain medications, and sick leave.[78] The program is currently being implemented in Canada,[21] Australia, and China. For more information on GLA:D and similar programs, including information on the content of the treatment programs, please refer to Skou and Roos,[78] the GLA:D website (https://www.glaid.dk/english.html), and Allen et al.[6]

A recent meta-analysis in hip OA found that exercise therapy with higher compliance to currently accepted recommendations on frequency, duration, and

intensity[36] was more effective in reducing pain compared to exercise therapy with uncertain compliance.[58] Other previous reviews have reported that the intensity and duration of the individual exercise sessions are seemingly less important for the treatment effects.[48,68] However, the details reported in most trials are not sufficient to actually evaluate the impact of intensity and duration of each session.[11] Therefore, we encourage more research in this area, with an emphasis on adhering to reporting guidelines such as the Consensus on Exercise Reporting Template[80] and the Template for Intervention Description and Replication checklist.[45]

Physical Activity and Inactivity in OA

Current physical activity guidelines recommend at least 150 minutes of moderate or 75 minutes of vigorous physical activity, in bouts of at least 10 minutes' duration, per week.[36] Helping people with OA become more physically active, along with participating in structured exercise therapy, is crucial, as the majority of people with hip and knee OA do not meet physical activity guidelines,[91] and are less active than their age-matched counterparts.[23] Importantly, physical inactivity in people with OA also increases their risk of a number of comorbidities[17] and functional decline, leading to higher health care costs.[28] As walking 150 minutes per week might not be tolerable for individuals with end-stage knee OA,[90] other types of physical activity, such as biking and walking with Nordic poles (walking poles specifically designed to be used to support a total-body version of walking) (**FIGURE 2**), might be preferable for this subgroup. Notably, fewer steps than the recommended 10 000 steps per day might be sufficient, as a recent study found that walking more than 6000 steps per day protected against developing functional impairments in people with or at risk of knee OA.[93]

Reduced physical activity levels in people with knee OA may be a key factor driving greater body mass index (BMI) in this group of people.[12] Highlighting a likely vicious cycle, risk of knee OA is also reported to increase exponentially with increasing BMI.[96] Importantly for people with knee OA, a 5% reduction in weight leads to moderate to large improvements in functional impairments,[19] and there is a dose-response relationship between percentage of weight loss and symptomatic improvement.[7] Although addressing dietary factors is a key component to achieving weight reduction,[19] increasing physical activity levels will also assist.[12,96] The relationship of hip OA with greater BMI is less clear,[39] but may still be important in some individuals.

Choice of intervention to improve symptoms and impairments may be the key to improving physical activity levels. Patient education and exercise therapy, including aerobic exercise, can have moderate positive effects on both symptoms and impairments,[48] even in people on a surgical wait list for joint replacement.[72,79,89] Physical activity, including exercise therapy, can also improve gait speed and lower-limb function, factors thought to be important to increasing physical activity levels.[82] However, while evidence suggests that there are small long-term improvements in physical activity levels following physical activity interventions in OA, a lack of consensus on methodology and outcome reporting severely hampers the conclusions that can be drawn on the effects on physical activity levels.[95] In severe hip and knee OA, total joint replacement is considered a cost-effective intervention to reduce symptoms and impairments.[29] However, some studies have reported only small increases in physical activity levels post surgery, despite large improvements in symptoms and impairments.[22,86] These findings highlight a possible need to promote and guide increases to physical activity levels following joint replacement surgery. Clearly, implementing exercise therapy and promoting physical activity in the management of people with hip and knee OA are vital to improving their physical activity levels and the broader health benefits this will lead to; however, more work is needed to support this notion.[95]

The Importance of Physical Activity and Exercise Therapy to Overall Health

Physical activity represents a cornerstone in the primary prevention of at least 35 chronic conditions,[17] and exercise therapy is considered first-line treatment in many chronic conditions.[64] Physical inactivity is regarded both as a cause and a consequence of OA and is associated with a number of diseases, such as CVD, type 2 diabetes, and dementia. Two out of 3 people with OA have comorbidities, including CVD, type 2 diabetes, and mental health conditions,[92] and people with hip and knee OA are at higher risk of all-cause mortality compared with the general population. The association of OA with CVD and dementia is particularly pronounced.[62] The benefits of physical activity and exercise therapy to people with hip and knee OA are, therefore, not limited to addressing symptoms and impairments, but can also decrease the risk and impact of comorbidities.

Inflammation: Linking OA and Comorbidity A number of chronic diseases, including CVD, type 2 diabetes, and dementia, are associated with OA and chronic low-grade inflammation.[64] Importantly, persistent systemic inflammation is associated with a high cardiovascular risk and predisposes one to metabolic disorders and muscle wasting.[13] Therefore, these

FIGURE 2. Woman walking with Nordic poles. Photo: Colourbox.com/Søren Thomsen.

disorders may lead to disability and decreased physical activity, exacerbating inflammation, and to the development of a number of chronic diseases, including OA, creating a "vicious cycle" of chronic inflammation (**FIGURE 3**).[13] Therefore, the anti-inflammatory effects[13] of exercise may contribute to explain the positive effects of physical activity and exercise therapy in many diseases.[13]

Cardiovascular Disease In developed countries, OA and CVD are the 2 most prevalent chronic conditions among people over the age of 70 years. Considering that OA is a leading cause of physical disability, including the ability to walk,[30,43] it will also likely reduce an individual's capacity for physical activity, and thus the capacity to prevent these chronic conditions. It is well established that regular physical activity decreases the risk for ischemic heart diseases and stroke.[73] Importantly, evidence has shown that symptomatic knee OA may increase the risk of stroke[46] and CVD, including ischemic heart disease and chronic heart failure.[41,67]

There are a number of reasons why physical activity and exercise therapy may prevent or treat CVD in people with OA. Both OA and CVD share common risk factors, including greater age and higher BMI.[64] Both conditions are also associated with chronic inflammation, and, as highlighted above, it is well documented that regular physical activity has anti-inflammatory effects.[13] Physical activity benefits with regard to protection against CVD also include training-induced increased fibrinolysis, decreased platelet aggregation, improved blood pressure regulation, optimized ratio of high-density to low-density lipoproteins, improved endothelium-mediated coronary vasodilation, increased heart rate variability, and improved glycemic control.[64]

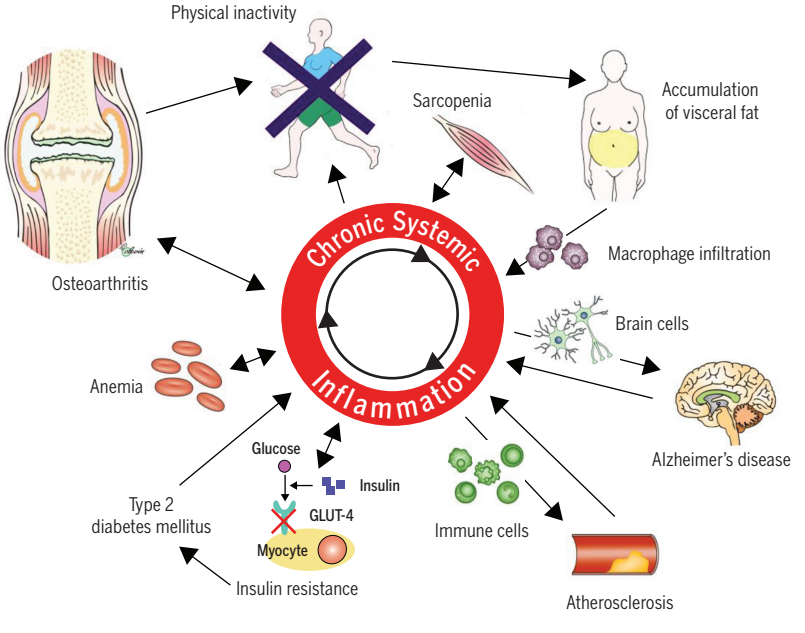

FIGURE 3. The "vicious cycle" of chronic inflammation (based on Figure 1 of Benatti and Pedersen[13]). In osteoarthritis, local inflammation of the synovial membranes of the knee (or hip) joint can lead to chronic systemic inflammation, which can predispose one to conditions that contribute to functional impairments, including insulin resistance, dyslipidemia, endothelial dysfunction, accelerated atherosclerosis, neurodegeneration, muscle atrophy, and anemia. Lack of physical activity and exercise, in turn, can cause the accumulation of visceral fat and thereby exacerbate inflammation and promote metabolic disorders, atherosclerosis, and the development of a number of chronic diseases. In a positive feedback loop, this will negatively affect cardiovascular performance and the ability to be physically active and exercise. Abbreviation: GLUT-4, glucose transporter type 4, insulin responsive.

Type 2 Diabetes Type 2 diabetes has been reported to be a risk factor for OA development in 2 meta-analyses.[55,94] It is less clear whether OA is a risk factor for type 2 diabetes development. However, physical inactivity that results from hip and knee OA[91] makes it likely, as this is a predisposing factor for type 2 diabetes development.[74] Regardless, promoting physical activity in people with OA in the presence of concurrent type 2 diabetes is important. There is international consensus that exercise therapy is 1 of the 3 cornerstones in the treatment of diabetes, along with diet and medication.[64] Physical activity and exercise therapy mediate their positive effects on the pathogenesis of type 2 diabetes via many mechanisms, including an effect on insulin sensitivity. Additionally, the role of inflammation in the pathogenesis of type 2 diabetes and associated complications is also well established,[27] meaning that it is likely that this population benefits from physical activity via its anti-inflammatory effect (**FIGURE 3**).[51]

Cognition and Neuropsychiatric Health Osteoarthritis is an independent risk factor for dementia,[47,87] and it is well established that physical activity decreases the risk of cognitive impairment and dementia.[35] Additionally, physical activity reduces neuropsychiatric symptoms in people with mild dementia,[44] improves dementia symptoms,[52] and improves the capacity to participate in activities of daily living.[64] Current research indicates that vascular and metabolic risk factors are the major players in cognitive impairment and dementia, including Alzheimer's disease.[84] However, physical activity might prevent dementia due to an effect on brain-derived neurotrophic factor, a growth factor for the hippocampus.[63]

Mental Health Osteoarthritis is associated with impaired mental health, high stress perception, and depression.[49] Evidence exists that physical activity may reduce symptoms of anxiety in people with chronic illnesses and improve symptoms associated with psychological stress

and depression.[64] The positive effect on mental disorders is thought to be multifactorial, and is beyond the scope of this commentary. The interested reader is recommended to consult other published reviews on this topic.[64,70]

Patient Education: The Missing Link to Ensure Long-Term Effects From Exercise Therapy?

Evidence of the benefits of exercise therapy for symptoms and impairments in individuals with hip and knee OA is substantial, and these benefits are sustained, at least to some extent, 6 months after ending the exercise therapy program.[33,34] However, benefits appear to decline over time following a program of supervised sessions,[33,34] and compliance is suggested to be the primary predictor of long-term exercise therapy outcomes in people with hip and knee OA.[69] Like most other noncurative treatments, including analgesia, exercise therapy effects will disappear when the individual does not continue the prescribed exercise regime at a sufficient dose, session duration, and intensity level. This holds true for OA-associated symptoms and impairments, as well as other benefits to prevention and management of the other chronic diseases mentioned above.

Education is recommended in most clinical practice guidelines for hip and knee OA,[60] and, together with booster supervised exercise therapy sessions,[1,65] may be important to improve compliance with physical activity and exercise therapy.[37] Education should include knowledge related to the causes and disease process of OA, including the influence of inactivity, effective and ineffective treatments, the importance of continuing physical activity, and self-help tools, such as guidance on how to self-manage symptoms. Patient knowledge will ensure that patients have more balanced expectations regarding their disease process and the importance of self-management, including understanding the important role of ongoing independent exercise therapy and booster sessions with a therapist to improve and maintain an acceptable symptom state.[61] Most importantly, this should facilitate continued physical activity participation, allowing better weight management and other health benefits. Beyond education and exercise therapy targeting disease-specific impairments, goal setting, activity monitoring (eg, wearable technology), and improving social support (eg, walking groups) should also be implemented in an attempt to improve activity levels and long-term adherence to exercise therapy in people with hip and knee OA.[38]

When the potential benefits[48] and harms[66] are compared, it is difficult to argue against the implementation of physical activity and exercise therapy for people with OA. However, some barriers and potential contraindications do exist. Key barriers to physical activity and exercise therapy in people with OA relate to fear of movement and pain flares. Fear-avoidance beliefs are common in individuals with OA and relate to impaired physical function.[42,81] A substantial number of people with OA fear that they may injure themselves as a result of physical activity participation.[40] Therefore, assistance in addressing fear of physical activity is essential to addressing physical inactivity and improving long-term adherence to exercise therapy. In most cases, reassurance to patients who may be fearful that exercise therapy can damage their joints should be provided.[26,71] It is vitally important that patients are well educated about potential pain flares and how to adjust their exercises should pain flares occur (see **FIGURE 1**). In cases of acute, severe joint inflammation, the affected joint may also need rest for a short period (2-3 days), and anti-inflammatories should be considered.[64] While patients with OA may experience pain flares from exercise therapy, the size of the flares will decrease with an increasing number of exercise sessions.[71] If needed, the nature of the exercise therapy can be changed for a period from, for example, land-based to water-based exercise therapy. Exercising joints other than the one(s) affected will also have a positive, clinical effect.[64]

Being severely overweight may be a relative contraindication for weight-bearing exercise therapy, as a mechanical overload may promote progression of the disease.[64] However, even in obese patients with knee OA, land-based exercise therapy can improve symptoms and impairments, with larger improvements seen when combining exercise therapy and weight loss.[56,57]

It may be necessary to educate young people with OA resulting from a joint injury to avoid or minimize participation in sports that involve heavy loading of the joints, especially with an axial compressive load or twisting (eg, basketball, football, handball, volleyball, high-intensity running, etc). Importantly, though, people with OA should be educated not to be fearful of other sports and physical activity in general, especially considering its potential health benefits. The overall weight of evidence indicates that even recreational running (not competitive) is not a risk factor for OA,[53] and it is seemingly associated with a lower occurrence of OA compared to having a sedentary lifestyle.[5]

CONCLUSION

Recommendations for the implementation of exercise therapy are hard to dispute in light of strong supporting evidence, reduced potential harms compared with other common OA treatments such as analgesia and surgery, and its beneficial effects on overall health. With the growing international burden of OA, embracing exercise therapy and promoting physical activity as first-line treatments offered to all people with hip and knee OA are essential. This clinical commentary provides a clear "call to action" for exercise therapy in hip and knee OA, along with key exercise therapy recommendations based on current evidence to help reduce future burden and costs.

REFERENCES

1. 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;45:975-983. https://doi.org/10.2519/jospt.2015.6015
2. Abbott JH, Robertson MC, Chapple C, et al. Manual therapy, exercise therapy, or both, in addition to usual care, for osteoarthritis of the hip or knee: a randomized controlled trial. 1: clinical effectiveness. *Osteoarthritis Cartilage*. 2013;21:525-534. https://doi.org/10.1016/j.joca.2012.12.014
3. Ageberg E, Link A, Roos EM. Feasibility of neuromuscular training in patients with severe hip or knee OA: the individualized goal-based NEMEX-TJR training program. *BMC Musculoskelet Disord*. 2010;11:126. https://doi.org/10.1186/1471-2474-11-126
4. Ageberg E, Roos EM. Neuromuscular exercise as treatment of degenerative knee disease. *Exerc Sport Sci Rev*. 2015;43:14-22. https://doi.org/10.1249/JES.0000000000000030
5. Alentorn-Geli E, Samuelsson K, Musahl V, Green CL, Bhandari M, Karlsson J. The association of recreational and competitive running with hip and knee osteoarthritis: a systematic review and meta-analysis. *J Orthop Sports Phys Ther*. 2017;47:373-390. https://doi.org/10.2519/jospt.2017.7137
6. Allen KD, Choong PF, Davis AM, et al. Osteoarthritis: models for appropriate care across the disease continuum. *Best Pract Res Clin Rheumatol*. 2016;30:503-535. https://doi.org/10.1016/j.berh.2016.09.003
7. Atukorala I, Makovey J, Lawler L, Messier SP, Bennell K, Hunter DJ. Is there a dose-response relationship between weight loss and symptom improvement in persons with knee osteoarthritis? *Arthritis Care Res (Hoboken)*. 2016;68:1106-1114. https://doi.org/10.1002/acr.22805
8. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med*. 2015;162:46-54. https://doi.org/10.7326/M14-1231
9. Bartels EM, Juhl CB, Christensen R, et al. Aquatic exercise for the treatment of knee and hip osteoarthritis. *Cochrane Database Syst Rev*. 2016;3:CD005523. https://doi.org/10.1002/14651858.CD005523.pub3
10. Bartholdy C, Juhl C, Christensen R, Lund H, Zhang W, Henriksen M. The role of muscle strengthening in exercise therapy for knee osteoarthritis: a systematic review and meta-regression analysis of randomized trials. *Semin Arthritis Rheum*. 2017;47:9-21. https://doi.org/10.1016/j.semarthrit.2017.03.007
11. Bartholdy C, Warming S, Nielsen SM, Christensen R, Henriksen M. Replicability of recommended exercise interventions for knee osteoarthritis: a descriptive systematic review of current clinical guidelines and recommendations [abstract]. *Osteoarthritis Cartilage*. 2017;25:S409-S410. https://doi.org/10.1016/j.joca.2017.02.706
12. Bauman A, Merom D, Bull FC, Buchner DM, Fiatarone Singh MA. Updating the evidence for physical activity: summative reviews of the epidemiological evidence, prevalence, and interventions to promote "active aging". *Gerontologist*. 2016;56 suppl 2:S268-S280. https://doi.org/10.1093/geront/gnw031
13. Benatti FB, Pedersen BK. Exercise as an anti-inflammatory therapy for rheumatic diseases—myokine regulation. *Nat Rev Rheumatol*. 2015;11:86-97. https://doi.org/10.1038/nrrheum.2014.193
14. Bennell KL, Dobson F, Roos EM, et al. Influence of biomechanical characteristics on pain and function outcomes from exercise in medial knee osteoarthritis and varus malalignment: exploratory analyses from a randomized controlled trial. *Arthritis Care Res (Hoboken)*. 2015;67:1281-1288. https://doi.org/10.1002/acr.22558
15. Bennell KL, Kyriakides M, Hodges PW, Hinman RS. Effects of two physiotherapy booster sessions on outcomes with home exercise in people with knee osteoarthritis: a randomized controlled trial. *Arthritis Care Res (Hoboken)*. 2014;66:1680-1687. https://doi.org/10.1002/acr.22350
16. Bennell KL, Wrigley TV, Hunt MA, Lim BW, Hinman RS. Update on the role of muscle in the genesis and management of knee osteoarthritis. *Rheum Dis Clin North Am*. 2013;39:145-176.
17. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol*. 2012;2:1143-1211. https://doi.org/10.1002/cphy.c110025
18. Chang AH, Lee SJ, Zhao H, Ren Y, Zhang LQ. Impaired varus–valgus proprioception and neuromuscular stabilization in medial knee osteoarthritis. *J Biomech*. 2014;47:360-366. https://doi.org/10.1016/j.jbiomech.2013.11.024
19. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis*. 2007;66:433-439. https://doi.org/10.1136/ard.2006.065904
20. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis*. 2014;73:1323-1330. https://doi.org/10.1136/annrheumdis-2013-204763
21. Davis AM, Kennedy D, Wong R, et al. Cross-cultural adaptation and implementation of Good Life with osteoArthritis in Denmark (GLA:D™): group education and exercise for hip and knee osteoarthritis is feasible in Canada. *Osteoarthritis Cartilage*. 2018;26:211-219. https://doi.org/10.1016/j.joca.2017.11.005
22. de Groot IB, Bussmann HJ, Stam HJ, Verhaar JA. Small increase of actual physical activity 6 months after total hip or knee arthroplasty. *Clin Orthop Relat Res*. 2008;466:2201-2208. https://doi.org/10.1007/s11999-008-0315-3
23. de Groot IB, Bussmann JB, Stam HJ, Verhaar JA. Actual everyday physical activity in patients with end-stage hip or knee osteoarthritis compared with healthy controls. *Osteoarthritis Cartilage*. 2008;16:436-442. https://doi.org/10.1016/j.joca.2007.08.010
24. Deshpande BR, Katz JN, Solomon DH, et al. Number of persons with symptomatic knee osteoarthritis in the US: impact of race and ethnicity, age, sex, and obesity. *Arthritis Care Res (Hoboken)*. 2016;68:1743-1750. https://doi.org/10.1002/acr.22897
25. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. *Lancet*. 2005;365:965-973. https://doi.org/10.1016/S0140-6736(05)71086-2
26. Dobson F, Bennell KL, French SD, et al. Barriers and facilitators to exercise participation in people with hip and/or knee osteoarthritis: synthesis of the literature using behavior change theory. *Am J Phys Med Rehabil*. 2016;95:372-389.
27. Donath MY. Targeting inflammation in the treatment of type 2 diabetes: time to start. *Nat Rev Drug Discov*. 2014;13:465-476. https://doi.org/10.1038/nrd4275
28. Dunlop DD, Semanik P, Song J, Manheim LM, Shih V, Chang RW. Risk factors for functional decline in older adults with arthritis. *Arthritis Rheum*. 2005;52:1274-1282. https://doi.org/10.1002/art.20968
29. Ferket BS, Feldman Z, Zhou J, Oei EH, Bierma-Zeinstra SM, Mazumdar M. Impact of total knee replacement practice: cost effectiveness analysis of data from the Osteoarthritis Initiative. *BMJ*. 2017;356:j1131. https://doi.org/10.1136/bmj.j1131
30. Fernandes GS, Valdes AM. Cardiovascular disease and osteoarthritis: common pathways and patient outcomes. *Eur J Clin Invest*. 2015;45:405-414. https://doi.org/10.1111/eci.12413
31. Fernandes L, Hagen KB, Bijlsma JW, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis*. 2013;72:1125-1135. https://doi.org/10.1136/annrheumdis-2012-202745
32. Fitzgerald GK, Fritz JM, Childs JD, et al. Exercise, manual therapy, and use of booster sessions in physical therapy for knee osteoarthritis: a multicenter, factorial randomized clinical trial. *Osteoarthritis Cartilage*. 2016;24:1340-1349. https://doi.org/10.1016/j.joca.2016.03.001
33. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev*. 2015;1:CD004376. https://doi.org/10.1002/14651858.CD004376.pub3
34. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S. Exercise for osteoarthritis of the hip. *Cochrane Database Syst Rev*. 2014:CD007912. https://doi.org/10.1002/14651858.CD007912.pub2
35. Gallaway PJ, Miyake H, Buchowski MS, et al. Physical activity: a viable way to reduce the risks of mild cognitive impairment, Alzheimer's

disease, and vascular dementia in older adults. *Brain Sci*. 2017;7:22. https://doi.org/10.3390/brainsci7020022

36. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011;43:1334-1359. https://doi.org/10.1249/MSS.0b013e318213fefb

37. Gay C, Chabaud A, Guilley E, Coudeyre E. Educating patients about the benefits of physical activity and exercise for their hip and knee osteoarthritis. Systematic literature review. *Ann Phys Rehabil Med*. 2016;59:174-183. https://doi.org/10.1016/j.rehab.2016.02.005

38. Greaves CJ, Sheppard KE, Abraham C, et al. Systematic review of reviews of intervention components associated with increased effectiveness in dietary and physical activity interventions. *BMC Public Health*. 2011;11:119. https://doi.org/10.1186/1471-2458-11-119

39. Grotle M, Hagen KB, Natvig B, Dahl FA, Kvien TK. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. *BMC Musculoskelet Disord*. 2008;9:132. https://doi.org/10.1186/1471-2474-9-132

40. Gunn AH, Schwartz TA, Arbeeva LS, et al. Fear of movement and associated factors among adults with symptomatic knee osteoarthritis. *Arthritis Care Res (Hoboken)*. 2017;69:1826-1833. https://doi.org/10.1002/acr.23226

41. Hall AJ, Stubbs B, Mamas MA, Myint PK, Smith TO. Association between osteoarthritis and cardiovascular disease: systematic review and meta-analysis. *Eur J Prev Cardiol*. 2016;23:938-946. https://doi.org/10.1177/2047487315610663

42. Heuts PH, Vlaeyen JW, Roelofs J, et al. Pain-related fear and daily functioning in patients with osteoarthritis. *Pain*. 2004;110:228-235. https://doi.org/10.1016/j.pain.2004.03.035

43. Hoeven TA, Leening MJ, Bindels PJ, et al. Disability and not osteoarthritis predicts cardiovascular disease: a prospective population-based cohort study. *Ann Rheum Dis*. 2015;74:752-756. https://doi.org/10.1136/annrheumdis-2013-204388

44. Hoffmann K, Sobol NA, Frederiksen KS, et al. Moderate-to-high intensity physical exercise in patients with Alzheimer's disease: a randomized controlled trial. *J Alzheimers Dis*. 2016;50:443-453. https://doi.org/10.3233/JAD-150817

45. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: Template for Intervention Description and Replication (TIDieR) checklist and guide. *BMJ*. 2014;348:g1687. https://doi.org/10.1136/bmj.g1687

46. Hsu PS, Lin HH, Li CR, Chung WS. Increased risk of stroke in patients with osteoarthritis: a population-based cohort study. *Osteoarthritis Cartilage*. 2017;25:1026-1031. https://doi.org/10.1016/j.joca.2016.10.027

47. Huang SW, Wang WT, Chou LC, Liao CD, Liou TH, Lin HW. Osteoarthritis increases the risk of dementia: a nationwide cohort study in Taiwan. *Sci Rep*. 2015;5:10145. https://doi.org/10.1038/srep10145

48. Juhl C, Christensen R, Roos EM, Zhang W, Lund H. Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-regression analysis of randomized controlled trials. *Arthritis Rheumatol*. 2014;66:622-636. https://doi.org/10.1002/art.38290

49. Jung JH, Seok H, Kim JH, Song GG, Choi SJ. Association between osteoarthritis and mental health in a Korean population: a nationwide study. *Int J Rheum Dis*. 2018;21:611-619. https://doi.org/10.1111/1756-185X.13098

50. Knoop J, van der Leeden M, Roorda LD, et al. Knee joint stabilization therapy in patients with osteoarthritis of the knee and knee instability: subgroup analyses in a randomized, controlled trial. *J Rehabil Med*. 2014;46:703-707. https://doi.org/10.2340/16501977-1809

51. Knudsen SH, Pedersen BK. Targeting inflammation through a physical active lifestyle and pharmaceuticals for the treatment of type 2 diabetes. *Curr Diab Rep*. 2015;15:82. https://doi.org/10.1007/s11892-015-0642-1

52. Lee HS, Park SW, Park YJ. Effects of physical activity programs on the improvement of dementia symptom: a meta-analysis. *Biomed Res Int*. 2016;2016:2920146. https://doi.org/10.1155/2016/2920146

53. Leech RD, Edwards KL, Batt ME. Does running protect against knee osteoarthritis? Or promote it? Assessing the current evidence. *Br J Sports Med*. 2015;49:1355-1356. https://doi.org/10.1136/bjsports-2015-094749

54. Lim BW, Hinman RS, Wrigley TV, Sharma L, Bennell KL. Does knee malalignment mediate the effects of quadriceps strengthening on knee adduction moment, pain, and function in medial knee osteoarthritis? A randomized controlled trial. *Arthritis Rheum*. 2008;59:943-951. https://doi.org/10.1002/art.23823

55. Louati K, Vidal C, Berenbaum F, Sellam J. Association between diabetes mellitus and osteoarthritis: systematic literature review and meta-analysis. *RMD Open*. 2015;1:e000077. https://doi.org/10.1136/rmdopen-2015-000077

56. Messier SP, Loeser RF, Miller GD, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. *Arthritis Rheum*. 2004;50:1501-1510. https://doi.org/10.1002/art.20256

57. 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;310:1263-1273. https://doi.org/10.1001/jama.2013.277669

58. Moseng T, Dagfinrud H, Smedslund G, Østerås N. The importance of dose in land-based supervised exercise for people with hip osteoarthritis. A systematic review and meta-analysis. *Osteoarthritis Cartilage*. 2017;25:1563-1576. https://doi.org/10.1016/j.joca.2017.06.004

59. National Center for Biotechnology Information. Exercise therapy. Available at: https://www.ncbi.nlm.nih.gov/mesh/?term=exercise+therapy. Accessed April 20, 2018.

60. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: the Chronic Osteoarthritis Management Initiative of the U.S. Bone and Joint Initiative. *Semin Arthritis Rheum*. 2014;43:701-712. https://doi.org/10.1016/j.semarthrit.2013.11.012

61. Nicolson PJ, Bennell KL, Dobson FL, Van Ginckel A, Holden MA, Hinman RS. Interventions to increase adherence to therapeutic exercise in older adults with low back pain and/or hip/knee osteoarthritis: a systematic review and meta-analysis. *Br J Sports Med*. 2017;51:791-799. https://doi.org/10.1136/bjsports-2016-096458

62. Nüesch E, Dieppe P, Reichenbach S, Williams S, Jüni P. All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. *BMJ*. 2011;342:d1165. https://doi.org/10.1136/bmj.d1165

63. Pajonk FG, Wobrock T, Gruber O, et al. Hippocampal plasticity in response to exercise in schizophrenia. *Arch Gen Psychiatry*. 2010;67:133-143. https://doi.org/10.1001/archgenpsychiatry.2009.193

64. Pedersen BK, Saltin B. Exercise as medicine – evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports*. 2015;25 suppl 3:1-72. https://doi.org/10.1111/sms.12581

65. Pisters MF, Veenhof C, van Meeteren NL, et al. Long-term effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a systematic review. *Arthritis Rheum*. 2007;57:1245-1253. https://doi.org/10.1002/art.23009

66. Quicke JG, Foster NE, Thomas MJ, Holden MA. Is long-term physical activity safe for older adults with knee pain?: A systematic review. *Osteoarthritis Cartilage*. 2015;23:1445-1456. https://doi.org/10.1016/j.joca.2015.05.002

67. Rahman MM, Kopec JA, Cibere J, Goldsmith CH, Anis AH. The relationship between osteoarthritis and cardiovascular disease in a population health survey: a cross-sectional study. *BMJ Open*. 2013;3:e002624. https://doi.org/10.1136/bmjopen-2013-002624

68. 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:CD010203. https://doi.org/10.1002/14651858.CD010203.pub2

69. Roddy E, Zhang W, Doherty M, et al. Evidence-based recommendations for the role of exercise in the management of osteoarthritis of the hip or knee—the MOVE consensus. *Rheumatology*

(Oxford). 2005;44:67-73. https://doi.org/10.1093/rheumatology/keh399

70. Salmon P. Effects of physical exercise on anxiety, depression, and sensitivity to stress: a unifying theory. *Clin Psychol Rev*. 2001;21:33-61. https://doi.org/10.1016/S0272-7358(99)00032-X

71. Sandal LF, Roos EM, Bøgesvang SJ, Thorlund JB. Pain trajectory and exercise-induced pain flares during 8 weeks of neuromuscular exercise in individuals with knee and hip pain. *Osteoarthritis Cartilage*. 2016;24:589-592. https://doi.org/10.1016/j.joca.2015.11.002

72. Saw MM, Kruger-Jakins T, Edries N, Parker R. Significant improvements in pain after a six-week physiotherapist-led exercise and education intervention, in patients with osteoarthritis awaiting arthroplasty, in South Africa: a randomised controlled trial. *BMC Musculoskelet Disord*. 2016;17:236. https://doi.org/10.1186/s12891-016-1088-6

73. Sesso HD, Paffenbarger RS, Jr., Lee IM. Physical activity and coronary heart disease in men: the Harvard Alumni Health Study. *Circulation*. 2000;102:975-980. https://doi.org/10.1161/01.CIR.102.9.975

74. Shah P, Shamoon F, Bikkina M, Kohl HW, 3rd. Medical cost of type 2 diabetes attributable to physical inactivity in the United States in 2012. *Diabetes Metab Syndr*. 2017;11:13-17. https://doi.org/10.1016/j.dsx.2016.06.020

75. Skou ST, Derosche CA, Andersen MM, Rathleff MS, Simonsen O. Nonoperative treatment improves pain irrespective of radiographic severity. A cohort study of 1,414 patients with knee osteoarthritis. *Acta Orthop*. 2015;86:599-604. https://doi.org/10.3109/17453674.2015.1029392

76. Skou ST, Odgaard A, Rasmussen JO, Roos EM. Group education and exercise is feasible in knee and hip osteoarthritis. *Dan Med J*. 2012;59:A4554.

77. Skou ST, Rasmussen S, Laursen MB, et al. The efficacy of 12 weeks non-surgical treatment for patients not eligible for total knee replacement: a randomized controlled trial with 1-year follow-up. *Osteoarthritis Cartilage*. 2015;23:1465-1475. https://doi.org/10.1016/j.joca.2015.04.021

78. Skou ST, Roos EM. Good Life with osteoArthritis in Denmark (GLA:D™): evidence-based education and supervised neuromuscular exercise delivered by certified physiotherapists nationwide. *BMC Musculoskelet Disord*. 2017;18:72. https://doi.org/10.1186/s12891-017-1439-y

79. Skou ST, Roos EM, Laursen MB, et al. A randomized, controlled trial of total knee replacement. *N Engl J Med*. 2015;373:1597-1606. https://doi.org/10.1056/NEJMoa1505467

80. Slade SC, Dionne CE, Underwood M, Buchbinder R. Consensus on Exercise Reporting Template (CERT): explanation and elaboration statement. *Br J Sports Med*. 2016;50:1428-1437. https://doi.org/10.1136/bjsports-2016-096651

81. Somers TJ, Keefe FJ, Pells JJ, et al. Pain catastrophizing and pain-related fear in osteoarthritis patients: relationships to pain and disability. *J Pain Symptom Manage*. 2009;37:863-872. https://doi.org/10.1016/j.jpainsymman.2008.05.009

82. Stubbs B, Hurley M, Smith T. What are the factors that influence physical activity participation in adults with knee and hip osteoarthritis? A systematic review of physical activity correlates. *Clin Rehabil*. 2015;29:80-94. https://doi.org/10.1177/0269215514538069

83. Thomeé R. A comprehensive treatment approach for patellofemoral pain syndrome in young women. *Phys Ther*. 1997;77:1690-1703. https://doi.org/10.1093/ptj/77.12.1690

84. Trigiani LJ, Hamel E. An endothelial link between the benefits of physical exercise in dementia. *J Cereb Blood Flow Metab*. 2017;37:2649-2664. https://doi.org/10.1177/0271678X17714655

85. Villadsen A, Overgaard S, Holsgaard-Larsen A, Christensen R, Roos EM. Immediate efficacy of neuromuscular exercise in patients with severe osteoarthritis of the hip or knee: a secondary analysis from a randomized controlled trial. *J Rheumatol*. 2014;41:1385-1394. https://doi.org/10.3899/jrheum.130642

86. Vissers MM, de Groot IB, Reijman M, Bussmann JB, Stam HJ, Verhaar JA. Functional capacity and actual daily activity do not contribute to patient satisfaction after total knee arthroplasty. *BMC Musculoskelet Disord*. 2010;11:121. https://doi.org/10.1186/1471-2474-11-121

87. Visuri T, Mäkelä K, Pulkkinen P, Artama M, Pukkala E. Long-term mortality and causes of death among patients with a total knee prosthesis in primary osteoarthritis. *Knee*. 2016;23:162-166. https://doi.org/10.1016/j.knee.2015.09.002

88. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2163-2196. https://doi.org/10.1016/S0140-6736(12)61729-2

89. Wallis JA, Taylor NF. Pre-operative interventions (non-surgical and non-pharmacological) for patients with hip or knee osteoarthritis awaiting joint replacement surgery – a systematic review and meta-analysis. *Osteoarthritis Cartilage*. 2011;19:1381-1395. https://doi.org/10.1016/j.joca.2011.09.001

90. Wallis JA, Webster KE, Levinger P, Singh PJ, Fong C, Taylor NF. The maximum tolerated dose of walking for people with severe osteoarthritis of the knee: a phase I trial. *Osteoarthritis Cartilage*. 2015;23:1285-1293. https://doi.org/10.1016/j.joca.2015.04.001

91. Wallis JA, Webster KE, Levinger P, Taylor NF. What proportion of people with hip and knee osteoarthritis meet physical activity guidelines? A systematic review and meta-analysis. *Osteoarthritis Cartilage*. 2013;21:1648-1659. https://doi.org/10.1016/j.joca.2013.08.003

92. Wesseling J, Welsing PM, Bierma-Zeinstra SM, et al. Impact of self-reported comorbidity on physical and mental health status in early symptomatic osteoarthritis: the CHECK (Cohort Hip and Cohort Knee) study. *Rheumatology (Oxford)*. 2013;52:180-188. https://doi.org/10.1093/rheumatology/kes288

93. White DK, Tudor-Locke C, Zhang Y, et al. Daily walking and the risk of incident functional limitation in knee osteoarthritis: an observational study. *Arthritis Care Res (Hoboken)*. 2014;66:1328-1336. https://doi.org/10.1002/acr.22362

94. Williams MF, London DA, Husni EM, Navaneethan S, Kashyap SR. Type 2 diabetes and osteoarthritis: a systematic review and meta-analysis. *J Diabetes Complications*. 2016;30:944-950. https://doi.org/10.1016/j.jdiacomp.2016.02.016

95. Williamson W, Kluzek S, Roberts N, et al. Behavioural physical activity interventions in participants with lower-limb osteoarthritis: a systematic review with meta-analysis. *BMJ Open*. 2015;5:e007642. https://doi.org/10.1136/bmjopen-2015-007642

96. Zhou ZY, Liu YK, Chen HL, Liu F. Body mass index and knee osteoarthritis risk: a dose-response meta-analysis. *Obesity (Silver Spring)*. 2014;22:2180-2185. https://doi.org/10.1002/oby.20835

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Long term efficacy of mobilisation with movement on pain and functional status in patients with knee osteoarthritis: a randomised clinical trial

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Abstract

Objectives: To evaluate the long term effect of mobilisation with movement on disability, pain and function in subjects with symptomatic knee osteoarthritis

Design: A randomised controlled trial.

Setting: A general hospital

Subjects: Forty adults with knee osteoarthritis (grade 1–3 Kellgren–Lawrence scale).

Interventions: The experimental group received mobilisation with movement and usual care (exercise and moist heat) while the control group received usual care alone in six sessions over two weeks.

Main Measures: The primary outcome was the Western Ontario McMaster University Osteoarthritis index, higher scores indicating greater disability. Pain intensity over 24 hours and during sit to stand were measured on a 10 centimetre visual analogue scale. Functional outcomes were the timed up and go test, the 12 step stair test, and knee range of motion. Patient satisfaction was measured on an 11 point numerical rating scale. Variables were evaluated blind pre- and post intervention, and at three and six months follow-up.

Results: Thirty five participants completed the study. At each follow-up including six-months, significant differences were found between groups favouring those receiving mobilisation with movement for all variables except knee mobility. The primary outcome disability showed a mean difference of 7.4 points (95% confidence interval, 4.5 to 10.3) at six-months and a mean difference of 13.6 points (95% confidence interval, 9.3 to 17.9) at three-months follow-up.

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Conclusion: In patients with symptomatic knee osteoarthritis, the addition of mobilisation with movement provided clinically significant improvements in disability, pain, functional activities and patient satisfaction six months later.

Keywords
Knee osteoarthritis, mobilisation with movement, manual therapy

Introduction

Pain and disability associated with knee osteoarthritis is the second most common musculoskeletal disorder with overall prevalence of 28.7%.[1] The disease burden to the individual and society as a whole for knee osteoarthritis is high.[2]

Symptoms associated with knee osteoarthritis are secondary to inflammation associated with structural damage[3] which primarily includes painful and restricted knee movements, as well reduced functional ability.[4] Altered knee joint mechanics[5] and associated neurosensory attrition[6] are considered as important in symptom progression.[7]

Various guidelines for the management of knee osteoarthritis include lifestyle modifications and exercise.[8] Exercise in particular has been shown to provide sustained benefits on pain and disability for at least six months.[9] However the parameters of exercise appears less important for recovery.[9]

Manual therapy can also be used as part of a multimodal conservative management approach for knee osteoarthritis as it has the potential to modify symptoms,[10] although the exact mechanism of action are unclear.[11] Differing to traditional passive manual therapy techniques, Mulligan manual therapy includes mobilisation with movement. This active form of treatment has demonstrated successful outcomes in the short-term[12,13] as well as preliminary evidence in the long-term in patients with knee osteoarthritis pain.[14]

The purpose of this study was to examine the long-term efficacy of mobilisation with movement in addition to usual care comprising exercise and heat in patients with symptomatic knee osteoarthritis. We hypothesised that compared to usual care; the addition of mobilisation with movement would induce greater pain reduction and improved function.

Methodology

An assessor blind randomised clinical trial evaluated the efficacy of mobilisation with movement in subjects with symptomatic knee osteoarthritis. The study was conducted at the physiotherapy department of Smt. Kashibai Navale Medical College and General Hospital, India between June 2018 and May 2019. Ethical approval was obtained from the ethical committee of the Smt. Kashibai Navale College of Physiotherapy (Approval number: SKNCOPT/IEC//2018/131). The trial was registered prospectively under the Clinical Trial Registry India (Registration number: CTRI/2018/03/012620, dated on 16/03/2018) and has been reported according to the recommendations of the Consolidated Standards of Reporting Trials statement. Trial completion occurred after data was collected from the final participant. No funding was received for this study.

Consecutive subjects with knee osteoarthritis presenting to the physiotherapy outpatient department were recruited into this trial. A diagnosis of knee osteoarthritis was made by an orthopaedic surgeon based on the American College of Rheumatology clinical criteria.[15] Subjects diagnosed with a score of between 1 and 3 on the Kellgren and Lawrence osteoarthritis scale[16] were considered for inclusion in the trial.

Subjects were assessed for eligibility based on inclusion and exclusion criteria. The inclusion criteria were as follows: Either gender, between 50 and 70 years of age with knee pain of duration greater than three months and intensity between 4 and 8 on a 10 centimetre visual analogue scale at the time of presentation. They were required to be able to stand up independently from a chair and to be able to lay prone. Subjects were excluded if they had recent lower limb fractures, any neurological condition, contraindication to manual therapy, post

traumatic knee osteoarthritis, total knee arthroplasty, uncontrolled hypertension, radiating leg pain and body mass index over 30.

Subjects were provided with an information sheet outlining the study. Those willing to participate were enrolled and asked to provide signed informed consent with the right to withdraw at any time. After recruitment, at initial assessment a qualified physiotherapist collected demographic data. Participants were then randomly and equally allocated to a group receiving mobilisation with movement plus exercise and moist heat (Experimental group) or a group receiving exercise and moist heat alone (Control group). Randomisation was achieved using a computer-generated sequence hidden in sequentially numbered opaque sealed envelopes by the treating therapist. All the subjects were asked not to reveal their group identity.

Interventions were provided individually by a physiotherapist with formal training in mobilisation with movement. To begin all subjects received moist heat for 15 minutes from a hydrocollator pack wrapped in soft towel applied around the affected knee.

Following this, an exercise programme was initiated. This programme was designed to improve muscle strength of the hip, knee and ankle musculature.[17] Exercises included pelvic bridging, resisted knee flexion and extension, mini squats and heel raises.[18] Pelvic bridging was performed against body weight resistance in crook lying, lifting the pelvis for five seconds. Knee flexion was performed in prone lying while knee extension was performed in sitting. Resistance was provided with a weighted ankle cuff commencing at 1 kilogram and progressing to 2 kilogram depending on the patient's comfort. Mini squat exercises were undertaken in standing and involved closed chain hip and knee flexion as far as comfort allowed. Single leg heel raise exercise was performed in standing against body weight resistance. Exercises were progressed from 15 repetitions $\times$ 3 sets to 20 repetitions $\times$ 5 sets as per the capability of the subject. All exercises were supervised during each session and exercise parameters were adjusted if required but without any modifications in the type of exercise. Recommendations were made for the patient to undertake similar exercise at home, however adherence was not formally checked. All subjects were advised to undertake brisk walking daily for 20 minutes.

In addition to exercise and moist heat, subjects in the intervention group received mobilisation with movement. This was applied to the affected knee prior to the exercise programme.[14] With the patient lying supine, the therapist applied a pain-free manual sustained glide force to the proximal tibia close to the knee joint (with counterforce on the femur) either in a lateral, medial, rotational, anterior or posterior direction. While this force was maintained, the subject was instructed to move their affected knee in the symptomatic direction, being either towards flexion or extension as far as possible without pain. The direction of glide which had the most beneficial effect on improving pain-free range of motion was chosen for the treatment. If the subject was able to achieve end range without pain, pain-free overpressure was applied by the therapist. The technique was progressed to weight-bearing once full range was achieved without pain in lying. Three sets of 6 to 10 repetitions of the successful mobilisation with movement were delivered in each session.

A self-applied mobilisation with movement, mimicking the therapist technique, was taught to the subjects in the first treatment session. Subjects were advised to perform self mobilisation with movement only if improvements in pain free range was achieved during its application. Subjects were allowed to alter the dose of self applied mobilisation with movement based on their pain pattern during daily activities. In cases of bilateral symptoms, the limb with the greatest pain was considered the affected limb to be treated. All subjects attended the clinic for six 45-minutes treatment sessions carried out over two consecutive weeks.

A qualified physiotherapist blind to the treatment condition evaluated all outcomes at base line, immediately post treatment (two weeks), as well as at three and six months post treatment. The primary outcome measure was the Western Ontario McMaster University Osteoarthritis index score.[19] The secondary outcome measures were the time required to complete the timed up and go test,[20]

knee range of motion,[21] pain intensity over the past 24 hours,[22] pain intensity while standing up from a sitting position,[22] time taken to complete the 12 step stair test[23] and patient satisfaction with treatment.

The Western Ontario McMaster University Osteoarthritis index score was used as a measure of disability. This questionnaire is composed of 24 items giving a maximum score of 96. The score is converted to a percentage where higher scores represents more severe disability. The minimal detectable change at 95% confidence interval is 16.1.[19] Average pain intensity over the past 24 hours, and pain intensity for sit to stand was assessed using a 10 centimetre visual analogue scale. The minimal detectable change is 0.08.[22] Higher values on a visual analogue pain scale indicate greater pain intensity. Knee range of motion was measured with a universal goniometer.[21] The timed up and go test was used to assess functional mobility. The time required to stand from a chair, walk 3 metres and sit again was measured in seconds. The average of two trials was recorded. The minimal detectable change for this test was reported as 1.10 seconds.[20] The 12 step test was used to measure functional mobility. The time required to climb and descend 12 steps was recorded, where shorter time duration to complete the test indicates better function. The minimal detectable change at 90% confidence interval is 2.33 seconds.[23] Patient satisfaction was measured using an 11-point numerical rating scale of satisfaction score with 0 indicating complete dissatisfaction while 10 completely satisfied. Scores were expressed as percentages.

Sample size was determined using statistical software G*Power 3.1. Considering an effect size of 0.20, with repeated measures Analysis of variance between group interactions, alpha level of 0.05, power (1-β) of 80%, the sample size required was 36. This was increased to 40 (20 subjects per group) in consideration of 10% dropping out.

Statistical analysis was performed using Statistical Package for the Social Sciences V23.0 (Statistical Package for the Social Sciences Inc., 444 N. Michigan Avenue, Chicago, Illinois, 60,611). As drop-outs were very low, according to intention-to-treat analysis, means from the remainder of the group were used for missing values.[24] Data was normally distributed according to visual inspection of histograms, and there were no outliers. Levene's test revealed homogeneity of variance ($P > 0.05$). Descriptive statistics were presented for each treatment group. Continuous variables were summarised with means and standard deviations. Categorical or dichotomous data were summarised with frequencies. A repeated measures General Linear Model (independent factor was group: usual care vs mobilisation with movement and repeated factor was time: pre to post intervention and at three and six months follow-up) was used to evaluate the differences in outcome variables. Variable included were the Western Ontario McMaster University Osteoarthritis index score, 24 hour knee pain, pain score during sit to stand, knee range of motion, timed up and go test, 12 step test time and patient satisfaction. Tukey's post hoc test was used to evaluate for significant differences in the main effect for group, time or interaction (group × time). The results are presented as the mean difference and 95% confidence interval for all outcomes across all time points. For all analyses, statistical tests were 2-tailed and the threshold of the P value considered as significant was set at <0.05.

Results

Forty participants (25 females) were recruited for this study. A chart indicating flow of participants and number of subjects dropping out through the study is shown in Figure 1. Genders were equally represented and subjects reported moderate levels of disability with moderate severity of pain (Table 1). No adverse effects were reported in this study. Group means for all outcome measures are presented in Table 2.

Between groups analysis revealed a significant effect of mobilisation with movement in favour of the experimental group for the Western Ontario McMaster University Osteoarthritis index score post intervention, at three-months follow-up, and at six-months follow-up (Table 3). Between groups

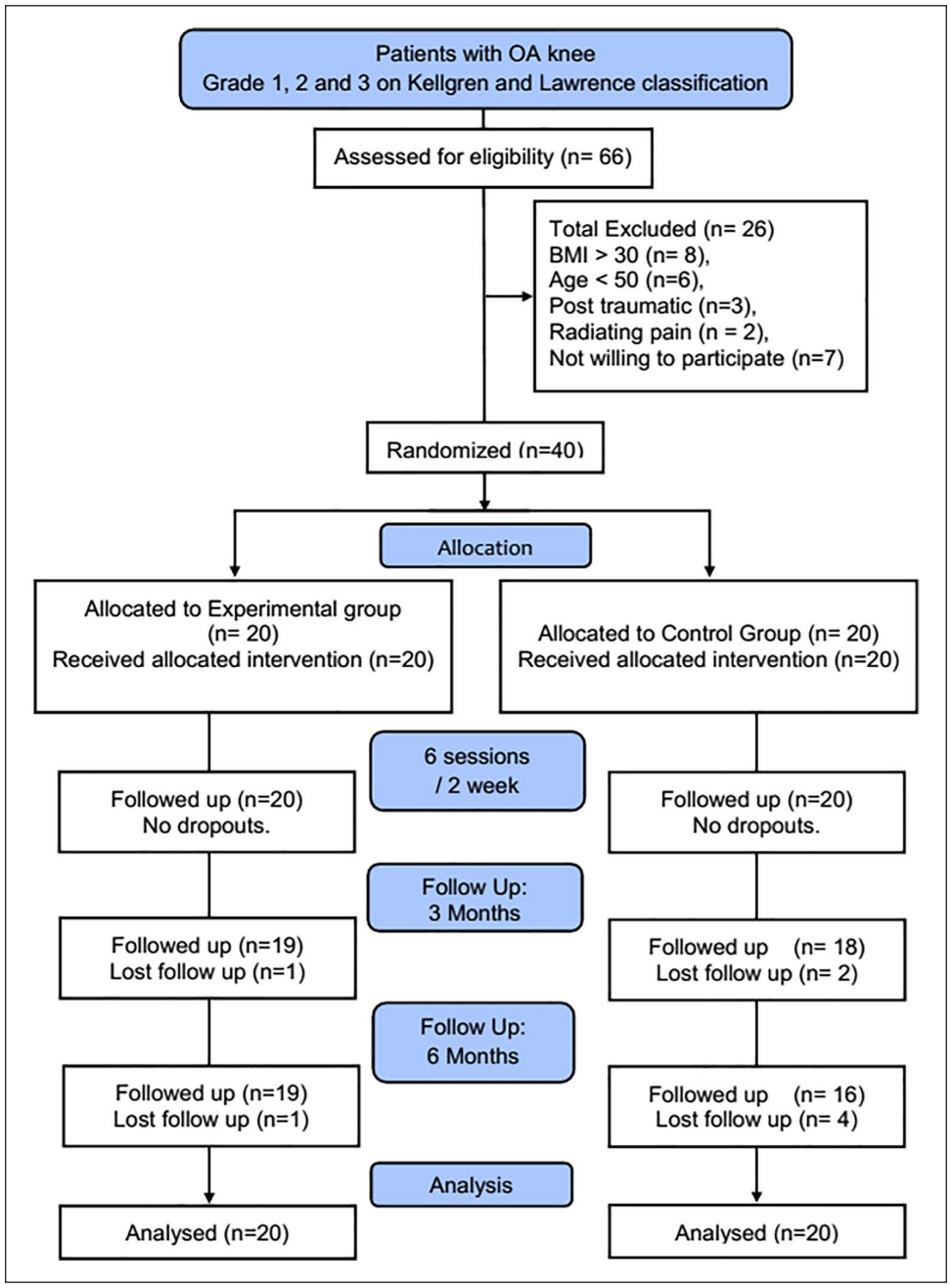

Figure 1. Flowchart of the participants through the study.

analysis for secondary outcome variables indicates a significantly greater improvement in the experimental group for knee pain score post intervention, as well as pain score for sit to stand and patient satisfaction at all time points. However there was no significant difference between the experimental

Table 1. Characteristics of participants.

Characteristic	Experimental group ($n = 20$)	Control group ($n = 20$)
Age (*year*), mean (SD)	58.5 (4.36)	59.4 (6.57)
Gender, *n* female (%)	12.0 (60.0%)	13.0 (65.0%)
BMI (kg/m^2), mean (SD)	26.2 (2.29)	25.6 (1.83)
Duration of symptoms (months), mean (SD)	9.6 (8.73)	9.8 (9.34)
Affected Knee *n*-Right (%)	10.0 (50.0%)	13.0 (65.0%)

group and control group for knee range of motion at all time points.

There was also no significant difference between the experimental and control groups for the timed up and go test and 12 step test post intervention. Despite this, a significant effect of mobilisation with movement was seen on these two variables at three- and six-months follow up (Table 3). There was a significant difference between groups for patient satisfaction measured by numeric rating scale expressed as a percentage post intervention (mean difference 41 points; 95% confidence interval, 32 to 49), at three-months follow-up (mean difference 27 points; 95% confidence interval, 17 to 37), and at six-months follow-up (mean difference1 7 points; 95% confidence interval, 20 to 24).

Discussion

In this randomised clinical trial, subjects receiving mobilisation with movement together with usual care showed significantly greater improvements in self-reported function, pain and patient satisfaction than those receiving usual care alone. This effect was apparent immediately after the intervention and was maintained even six-months later. However, there were no significant differences between groups for functional mobility as measured with the timed up and go test and 12 steps test immediately after the intervention. Significant beneficial differences were apparent favouring the experimental group in these variables at three- and six-months follow-up. These results are consistent with previous studies investigating the efficacy of mobilisation with movement for the management of symptomatic knee osteoarthritis.[12–14,25,26]

The improvement seen in both groups is likely partly explained by the positive effects of exercise. A Cochrane systematic review conducted by Fransen et al.[9] provides high to moderate quality evidence for the beneficial effects of exercise in knee osteoarthritis.[9] Exercise reduces pain, increases muscle strength and improves control around the affected joint. Exercise also potentially has disease-modification effects by increasing proteoglycan content of cartilage, increasing its thickness and reducing the rate of joint space narrowing.[10,27,28]

The greater pain reduction in the experimental group compared to the control group could be explained by modulation of pain through various mechanisms. Mobilisation with movement may decrease nociceptive inputs while at the same time increasing non-nociceptive inputs via activation of peripheral mechanoreceptors. In addition central mechanisms are involved as there is activation of the non-opioid mediated descending pain inhibitory system.[11] Effects could also be mediated by altered output mechanisms such as changes to muscle activation and behavioural mechanisms.[29]

Knee range of motion improved significantly following the intervention and at three-months follow-up in both groups, however, there was no further improvement after this in the experimental group. A possible explanation could be that full range of motion, similar to the relatively unaffected knee, was achieved at the end of three-months and the effects were sustained at final reassessment point. These results are in accordance with previous studies utilising mobilisation with movement.[13,14,25,26,30] The experimental group regained full range of motion much earlier, suggesting a quicker time to recovery.

Table 2. Mean (SD) for all outcome measures at baseline, two weeks, three and six months for each group.

Outcome measure	Groups mean (SD) *n* = 20							
	Week 0		Week 2		Three months		Six months	
	Exp G	C G	Exp G	C G	Exp G	C G	Exp G	C G
WOMAC score /100	62.6 (9)	61.0 (9.7)	41.4 (8.2)	55.6 (8.9)	25.3 (5.6)	38.9 (7.4)	21.6 (3.4)	29.0 (5.7)
24 hour Knee pain On VAS/10	6.4 (1.4)	6.3 (1.3)	3.2 (1.2)	5.3 (1.7)	2.3 (1)	4.2 (1.2)	2.0 (0.8)	4.0 (1.1)
Pain while Sit to stand on VAS/10	7.4 (1.6)	6.7 (1.4)	4.2 (1.4)	5.4 (1.9)	3.3 (1.3)	4.9 (1.6)	3.1 (1.3)	4.5 (1.6)
Affected knee total ROM°	118.2 (14)	121.6 (9.1)	126.8 (11.9)	123.7 (9.1)	131.1 (10.1)	127.6 (8.2)	131.1 (10)	126.6 (7.8)
Relatively unaffected knee total ROM°	127.8 (10.7)	132.0 (8.9)	NA	NA	NA	NA	NA	NA
Timed up go sec	15.4 (5.9)	12.4 (1.7)	12.4 (5)	11.9 (1.6)	9.5 (1.9)	11.6 (1.5)	8.6 (0.9)	10.8 (1.3)
12 step test sec	25.3 (6.8)	24.3 (5)	19.8 (4.7)	19.9 (4.7)	13.8 (2.6)	20.1 (3)	12.1 (2.4)	16.8 (1.9)
Patient satisfaction on NRS/10 expressed in %	NA	NA	68.0 (14.0)	28.0 (10.0)	84.0 (17.0)	57.0 (12.0)	96.0 (7.0)	79.0 (14.0)

Exp G: Experimental group; C G: Control group; WOMAC: Western Ontario McMaster University Osteoarthritis index; VAS: Visual analogue scale; ROM: Range of motion; NRS: Numeric rating scale.

Table 3. Within-group and between-group mean differences (95% CI).

Outcome measure	Within-group difference MD (95% CI) *n* = 20						Between-group difference MD (95% CI) *n* = 20		
	Week 2 versus week 0		Three months versus two weeks		Six months versus three months		Week 2	Three months	Six months
	Exp G	C G	Exp G	C G	Exp G	C G	Exp G–C G	Exp G–C G	Exp G–C G
WOMAC score /100	21.2 (16.4–25.9)	5.4 (2.5–8.4)	16.1 (11.4–20.7)	16.6 (13.2–20.0)	3.7 (1.8–5.6)	9.9 (6.8–13.0)	14.1 (8.5–19.7)	13.6 (9.3–17.9)	7.4 (4.5–10.3)
24hour Knee pain VAS/10	3.3 (2.7–3.9)	1.0 (0.5–1.6)	0.9 (0.4–1.3)	1.0 (0.5–1.6)	0.3 (0.0–0.5)	0.3 (0.1–0.4)	2.1 (1.0–3.2)	2.0 (1.1–2.8)	2.0 (1.3–2.6)
Pain while Sit to stand VAS/10	3.1 (2.6–3.7)	1.3 (0.4–2.2)	1.0 (0.6–1.3)	0.5 (0.1–0.9)	0.2 (0.1–0.3)	0.4 (0.1–07)	1.2 (0.1–2.2)	1.7 (0.8–2.5)	1.4 (0.5–2.3)
Total knee ROM Degrees	8.7 (11.8–5.6)	2.1 (4.2–0)	4.3 (6.8–1.7)	3.9 (7.5–0.3)	0.0 (0.0–0.0)	0.7 (0.8–2.6)	3.2 (–9.0–2.6)	0.5 (–0.1–1.1)	4.5 (–10.1–1.1)
Timed up go sec	3.1 (2.1–4.0)	0.5 (0.1–0.9)	2.9 (0.8–5.1)	0.2 (0.0–0.5)	0.9 (0.0–1.8)	0.8 (0.2–1.4)	0.6 (–2.9–1.8)	2.1 (1.0–3.2)	2.2 (1.5–2.9)
12 Step test sec	5.5 (3.7–7.2)	2.4 (0.7–4.2)	6.1 (4.1–8.0)	1.3 (0.5–2.2)	1.7 (0.9–2.6)	3.8 (2.2–5.3)	2.1 (–0.9–5.1)	6.8 (4.7–8.9)	4.7 (3.3–6.1)

Exp G: Experimental group; C G: Control group; WOMAC: Western Ontario McMaster University Osteoarthritis index; VAS: Visual Analogue Scale; NRS: Numeric rating Scale.

For the timed up and go test and 12 steps test the difference between experimental and control groups was evident only after three months. One explanation for this is that pain reduction achieved with mobilisation with movement may not have been sufficient to achieve an immediate improvement in these functional activities. These more vigorous activities are not only impaired by pain but also by other factors such as muscle weakness. Muscle strength may have improved over time with repetition during resumption of normal functional activities and could explain improvement seen in the experimental group after three months.[31]

Strengths of this study are the relatively long follow-up period of six-months as well as the broad mix of patients attending a typical general hospital physiotherapy clinic. Previous reports show no benefit for exercise combined with passive manual therapy over exercise alone for knee osteoarthritis.[32,33] However one study reports significant short-term improvements in disability post-intervention for mobilisation with movement and exercise.[26] This disparity in effects may be explained by the functional nature of mobilisation with movement, which incorporates progressive active weight-bearing movements in the treatment of disability associated with knee osteoarthritis. This progressive approach combined with home exercise may reduce fear of movement and improve self-efficacy.

It is important to recognise the limitations of our study. First, the sample size was small, despite being adequately powered, increasing the risk of false positive findings. In addition, there was no group receiving no treatment or 'wait and see', hence improvement seen in the usual care group could be related to natural resolution. As well, we did not include a placebo group which could have helped to understand the true effects of mobilisation with movement as there is contrasting evidence on its efficacy over a placebo response in the management of knee osteoarthritis.[12,13] A further limitation is that we trusted the verbal feedback for ensuring the subjects adherence to the home exercise protocol. We did not evaluate adherence. Finally, there was some heterogeneity in the population in terms of unilateral and bilateral knee osteoarthritis.[34] This could have impacted the results, particularly functional activities such as the timed up and go test.

Future studies evaluating long-term efficacy of mobilisation with movement should be conducted with a large population ideally with a placebo arm. Future research may focus on possibilities of effective ways to enhance the beneficial effects of mobilisation with movements in chronic conditions like knee osteoarthritis.

Our study highlights that a short period of Mulligan manual therapy combined with a simple supervised exercise programme can have a significant clinically relevant effect on improving outcomes in patients with typical symptomatic knee osteoarthritis.

In conclusion, subjects with symptomatic knee osteoarthritis receiving two-weeks of mobilisation with movement in addition to usual care had significantly greater improvements than those receiving usual care alone. Beneficial effects were seen in disability, pain, function and patient satisfaction and were sustained for six months.

Clinical message

- Six sessions of mobilisation with movement combined with exercise over two weeks improved disability, functional activities and pain at six months in people suffering from symptomatic knee osteoarthritis.

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Nil.

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Analysis/interpretation: Toby Hall, Kiran Satpute, Aishwarya Nigam
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Declaration of conflicting interests

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References

1. Pal C, Singh P, Chaturvedi S, et al. Epidemiology of knee osteoarthritis in India and related factors. *Indian J Orthop* 2016; 50(5): 518.
2. Losina E, Silva GS, Smith KC, et al. Quality adjusted life years lost due to physical inactivity in the United States osteoarthritis population. *Arthritis Care Res*. Epub ahead of print 26 July 2019. DOI: 10.1002/acr.24035.
3. Neogi T. Structural correlates of pain in osteoarthritis. *Clin Exp Rheumatol* 2017; 35 Suppl. 107(5): 75–78.
4. Stefanik JJ, Duncan R, Felson DT, et al. Diagnostic performance of clinical examination measures and pain presentation to identify patellofemoral joint osteoarthritis. *Arthritis Care Res* 2018; 70(1): 157–161.
5. Hamai S, Moro-oka T, Miura H, et al. Knee kinematics in medial osteoarthritis during in vivo weight-bearing activities. *J Orthop Res* 2009; 27(12): 1555–1561.
6. McDougall JJ. Osteoarthritis is a neurological disease – an hypothesis. *Osteoarthr Cartil Open* 2019; 1(1–2): 100005.
7. Felson DT. Osteoarthritis as a disease of mechanics. *Osteoarthritis Cartilage*. 2013; 21(1): 10–15.
8. Jonsson T, Eek F, Dell'Isola A, et al. The better management of patients with osteoarthritis program: outcomes after evidence-based education and exercise delivered nationwide in Sweden. Pan F, editor. *PLoS One* 2019; 14(9): e0222657.
9. Fransen M, McConnell S, Harmer AR, et al. Exercise for osteoarthritis of the knee: a Cochrane systematic review. *Br J Sports Med* 2015; 49(24): 1554–1557.
10. Leong DJ and Sun HB. Osteoarthritis – why exercise? *J Exerc Sports Orthop* 2013; 1(1): 04.
11. Bialosky JE, Beneciuk JM, Bishop MD, et al. Unraveling the mechanisms of manual therapy: modeling an approach. *J Orthop Sports Phys Ther* 2018; 48(1): 8–18.
12. Bhagat M, Neelapala YVR and Gangavelli R. Immediate effects of Mulligan's techniques on pain and functional mobility in individuals with knee osteoarthritis: a randomized control trial. *Physiother Res Int* 2020; 25(1): e1812.
13. Alkhawajah HA and Alshami AM. The effect of mobilization with movement on pain and function in patients with knee osteoarthritis: a randomized double-blind controlled trial. *BMC Musculoskelet Disord* 2019; 20(1): 452.
14. Kaya Mutlu E, Ercin E, Razak Ozdıncler A, et al. A comparison of two manual physical therapy approaches and electrotherapy modalities for patients with knee osteoarthritis: a randomized three arm clinical trial. *Physiother Theory Pract* 2018; 34(8): 600–612.
15. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986; 29: 1039–1049.
16. Kellgren JH and Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957; 16(4): 494–502.
17. Page CJ, Hinman RS and Bennell KL. Physiotherapy management of knee osteoarthritis. *Int J Rheum Dis* 2011; 14: 145–151.
18. Fernandez de las Penas C, Cleland J and Dommerholt J (eds). *Manual therapy for musculoskeletal pain syndromes an evidence- and clinical-informed approach*. 1st ed. China: Elsevier, 2016, p.486.
19. Williams VJ, Piva SR, Irrgang JJ, et al. Comparison of reliability and responsiveness of patient-reported clinical outcome measures in knee osteoarthritis rehabilitation. *J Orthop Sports Phys Ther* 2012; 42(8): 716–723.
20. Alghadir A, Anwer S and Brismée J-M. The reliability and minimal detectable change of Timed Up and Go test in individuals with grade 1 – 3 knee osteoarthritis. *BMC Musculoskelet Disord* 2015; 16(1): 174.
21. Milanese S, Gordon S, Buettner P, et al. Reliability and concurrent validity of knee angle measurement: smart phone app versus universal goniometer used by experienced and novice clinicians. *Man Ther* 2014; 19(6): 569–574.
22. Alghadir A, Anwer S, Iqbal A, et al. Test retest reliability, validity, and minimum detectable change of visual analogue, numerical rating, and verbal rating scales for measurement of osteoarthritic knee pain. *J Pain Res* 2018; 11: 851–856.
23. Dobson F, Hinman RS, Hall M, et al. Reliability and measurement error of the Osteoarthritis Research Society International (OARSI) recommended performance-based tests of physical function in people with hip and knee osteoarthritis. *Osteoarthritis Cartilage* 2017; 25(11): 1792–1796.
24. Armijo-Olivo S, Warren S and Magge D. Intention to treat analysis, compliance, drop-outs and how to deal with missing data in clinical research: a review. *Phys Ther Rev* 2009; 14: 36–49.
25. Ughreja RA and Shukla YU. Mulligan's Mobilization with Movement (MWM) relieves pain and improves functional status in osteoarthritis knee. *Int J Physiother* 2017; 4(2): 132–138.
26. Rao RV, Balthillaya G, Prabhu A, et al. Immediate effects of Maitland mobilization versus Mulligan Mobilization

with movement in osteoarthritis knee- a randomized crossover trial. *J Bodyw Mov Ther* 2018; 22(3): 572–579.
27. Vincent KR and Vincent HK. Resistance exercise for knee osteoarthritis. *PM R* 2012; 4: S45– S52.
28. Ericsson YB, Roos EM, Owman H, et al. Association between thigh muscle strength four years after partial meniscectomy and radiographic features of osteoarthritis 11 years later. *BMC Musculoskelet Disord* 2019; 20(1): 512.
29. Hing W, Hall T and Mulligan B. *The Mulligan concept of manual therapy*. 2nd ed. Chatswood, NSW: Elsevier, 2019, pp.1–19.
30. Takasaki H, Hall T and Jull G. Immediate and short-term effects of Mulligan's mobilization with movement on knee pain and disability associated with knee osteoarthritis – a prospective case series. *Physiother Theory Pract* 2013; 29(2): 87–95.
31. Liu C, Shiroy D, Jones L, et al. Systematic review of functional training on muscle strength, physical functioning, and activities of daily living in older adults. *Eur Rev Aging Phys Act* 2014; 11: 95–106.
32. 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; 45(12): 975–983.
33. 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; 38(1): 1–21.e2.
34. Riddle D and Stratford P. Unilateral vs bilateral symptomatic knee osteoarthritis: associations between pain intensity and function. *Rheumatology* 2013; 52: 2229–2237.

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RESEARCH ARTICLE

WILEY

Immediate effects of Mulligan's techniques on pain and functional mobility in individuals with knee osteoarthritis: A randomized control trial

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Abstract

Background and Purpose: Mulligan's mobilization with movement was shown to be effective when implemented in multimodal therapy for knee osteoarthritis. However, no study has evaluated the Mulligan's technique in isolation and compared the relative effectiveness with sham-controlled interventions. Hence, the present study examined the immediate effects of Mulligan's techniques with sham mobilization on the numerical pain rating scale (NPRS) and timed up and go (TUG) test in individuals with knee osteoarthritis.

Methods: Thirty participants (mean age: 55.3 ± 8.3 years) with symptoms at the knee and radiographic diagnosis of knee osteoarthritis were randomized into sham (n = 15) and intervention (n = 15) groups. The intervention (I) group received Mulligan's mobilization glides that resulted in relative pain relief for three sets of 10 repetitions. For the sham (S) group, the therapist's hand was placed over the joint surfaces mimicking the pain-relieving glides, without providing the gliding force. The outcome measures NPRS and TUG were recorded by a blinded assessor pre- and post-intervention.

Results: Statistically significant differences were identified between the groups in post-intervention median (interquartile range) NPRS (I group: 4.00 [2.00–5.00]; S group: 6.00 [4.00–7.00]) and TUG scores (I group: 10.9 [9.43–10.45]; S group: 13.18 [10.38–16.00]) with the intervention group demonstrating better outcomes (p < .05). Within-group, the post-intervention scores of NPRS and TUG were significantly lower (p < .05) compared to the pre-intervention scores in the intervention group. In the sham group, a statistically significant pre–post change was noticed only in the NPRS scores but not in the TUG scores.

Conclusion: Mulligan's techniques were effective in improving pain and functional mobility in individuals with knee osteoarthritis. The underlying mechanisms for observed effects must be examined further, as participants reported pain relief following sham mobilization.

KEYWORDS

arthralgia, manual therapies, physical therapy techniques, sham treatment

"This Manuscript has not been published elsewhere, and it has not been submitted simultaneously for publication elsewhere."

Trial registration no: CTRI/2017/03/008073

1 | INTRODUCTION

The Global Burden of Disease Study conducted in 2010 ranked hip and knee osteoarthritis (OA) as the 11th highest contributors to disability among 129 musculoskeletal conditions (Cross et al., 2014). The global age-standardized prevalence of knee OA was reported as 3.8% with a higher female preponderance (Cross et al., 2014). The clinical features of knee OA include joint pain, stiffness, crepitation, and restricted range of motion causing functional limitations in walking, squatting, and sit to stand activities (Bijlsma, Berenbaum, & Lafeber, 2011). Treatment guidelines by American College of Rheumatology and The European League against Rheumatism recommend physical therapy interventions in the non-pharmacological management of knee OA. Physical therapy approaches include aquatic therapy, land-based resistance training, muscle stretching, footwear modifications, taping, electrotherapy, and manual therapy (Fernandes et al., 2013; Hochberg et al., 2012).

Manual therapy is a conditionally recommended treatment option by American College of Rheumatology for knee OA with moderate to severe chronic knee pain and when joint replacement and other surgical procedures are not suitable (Hochberg et al., 2012). Recent systematic reviews identified low to moderate level of evidence for short term and long term effects of manual therapy in knee OA (French, Brennan, White, & Cusack, 2011; Xu *et al*., 2017). Mulligan's Mobilization with Movement (MWM) advocates therapist-applied accessory gliding force combined with active movement (Mulligan, 1993). The goal of MWM is to achieve immediate pain relief possibly by regulation of the non-opioid pain sensory pathways and by correction of mispositional faults (Paungmali, O'Leary, Souvlis, & Vicenzino, 2004). These positional faults may result from changes in the shape of articular surfaces, cartilage thickness, fibre orientation in the capsule-ligamentous complex, and the direction of musculo-tendinous pull, causing altered mechanics in the osteoarthritic knees (Baker, Nasypany, Seegmiller, & Baker, 2013).

Previous studies have found positive results using MWM in knee OA. Mutlu et al.2018, found that the combination of conventional exercise with MWMs or passive joint mobilization and electrotherapy were equally effective in reducing pain as compared with electrotherapy after 1 year follow-up. The case series by Takasaki, Hall, & Jull, 2013, found immediate improvements after Mulligan's mobilization alone, on passive knee flexion range of motion and knee pain scores. Another randomized crossover study by Rao et al. (2018) found equal effectiveness of Mulligan's and Maitland mobilization techniques on knee pain, function, and pain-free squat angle.

Few kinematic studies on medial knee OA participants have identified abnormal tibiofemoral mechanics such as reduced internal rotation while performing knee flexion and laterally shifted tibia during knee extension (Saari et al., 2005; Moro-oka, T.A et al., 2008, Hamai et al., 2009). MWM is hypothesized to correct these abnormal mechanics by delivering manual translational and rotational glides while the movement is performed. On the contrary, several non-specific effects of manual therapy techniques such as the influence of touch and patient's beliefs have also been proposed (Bialosky, Bishop, Price, Robinson, & George, 2009).

In general, the inclusion of a sham or placebo control group allows the differentiation of specific and non-specific effects of treatment techniques (Hancock, Maher, Latimer, & McAuley, 2006). Therefore, comparing Mulligan's techniques with sham intervention may provide an insight into the underlying mechanisms for their clinical effectiveness and enables to differentiate between the role of tactile input and directional forces (correcting positional faults) in achieving pain relief in knee OA. Also, the outcome measures in rheumatology III initiative emphasizes the use of functional outcome measures in the clinical trials on participants with OA (Chiarotto, Ostelo, Turk, Buchbinder, & Boers, 2017). Therefore, as a proof of concept, the current study compared the immediate effects of Mulligan's techniques with sham mobilization on knee pain (numerical pain rating scale) and functional mobility (timed up and go test).

2 | METHODS

2.1 | Study design

A randomized, double-blinded, sham-controlled, parallel-group design trial with a 1:1 allocation ratio was conducted on individuals with knee OA at the Department of Physiotherapy.

2.2 | Participants

Individuals referred for physiotherapy with a clinical and radiological diagnosis of knee OA were informed about the study and screened for recruitment. The participants had to meet the following inclusion criteria: age more than 45 years, pain and crepitus in the knee joint during knee movements, duration of pain more than 3 months, and radiological tibiofemoral degeneration with Grades 1–3 according to the Kellgren and Lawrence classification (Kellgren & Lawrence, 1957) with bilateral involvement.

Participants with a systemic or local infection, OA secondary to rheumatoid and other inflammatory and autoimmune conditions, acute trauma and fractures in the past 6 months, patellofemoral pain (screened using Clarke's test), and unavailability of radiographs were excluded. Eligible participants were explained about the study procedure, and written informed consent was obtained from the subjects who were willing to participate.

2.3 | Sample size, randomization, allocation, and blinding

The sample size for the study was calculated at 5% level of significance and 80% power. In order to achieve a minimal clinically important difference of 2.0 points on the Numerical Pain Rating Scale using the formula for comparison of means (Farrar, Young, LaMoreaux, Werth, & Poole, 2001), the sample size was found to be a total of 30 with 15 participants in each group.

A random sequence of numbers from 1–30 was generated from the website www.random.org using the simple randomization method (Haahr, 2012; Ribeiro, de Castro, Sole, & Vicenzino, 2016). After the participant recruitment, a volunteer revealed group allocation (intervention and sham groups) to the investigator, opening the sequentially numbered opaque sealed envelopes that were used for allocation concealment.

The participants were informed that they would be allotted to one of the two similar intervention groups of the study. The exact nature of the intervention in the allocated group was not disclosed. The intervention for both the groups was delivered by the investigator, who has completed a certified course in Mulligan's techniques. Outcome measures were administered and recorded by another physiotherapist who was unaware of the group allocation. Thus, the participants and the outcome assessor were blinded to the group allocation (double-blinded). The radiological grade of knee OA was recorded, and the offending (painful) knee movement (flexion or extension) was identified according to the participant's subjective report.

2.4 | Procedure

The accessory glides were performed during the testing procedure in the intervention group in a predetermined sequence of gliding directions, with specific hand placements as described below (Mulligan, 1993):

1 Medial rotational: The investigator grasped the proximal tibia of the participants with both hands and provided a medially directed torsional force resulting in the medial rotation (Figure 1).

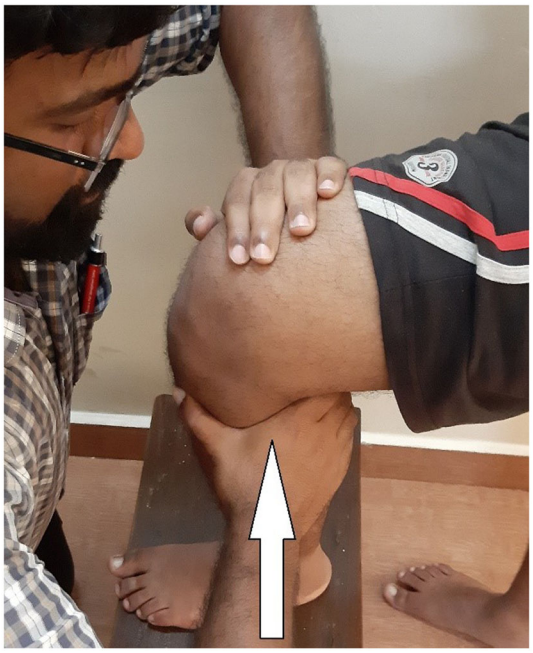

FIGURE 1 Medial translational glide of tibia in weight bearing

2 Lateral rotational: The investigator grasped the proximal tibia of the participants with both hands and provided a laterally directed torsional force resulting in lateral rotation.

3 Medial translational: The investigator stabilized the distal femur of the participants on the medial aspect with one hand and applied a medially directed translational force with the other hand placed on the lateral aspect of the proximal tibia (Figure 2).

4 Lateral translational: The investigator stabilized the distal femur on the lateral aspect with one hand and applied a laterally directed translational force with the other hand, placed on the medial aspect of the proximal tibia.

The MWM's were performed in either weight-bearing or non-weight bearing positions. While weight-bearing, the participants placed the lower extremity with the more painful knee on a low stool and stepped up or lunged forward if the offending movement was extension or flexion, respectively. The participants received support as desired, using their hands from adjacent plinth while performing the instructed movement. Before initiation of the painful movement, an accessory glide was delivered, and the force was sustained until return to the starting position. If pain relief was not achieved in weight-bearing, the glides were performed in a non-weight bearing position during composite hip and knee flexion/extension in supine lying. Three trials of each glide were given, and the glide direction that minimized or relieved the pain was chosen for the intervention.

The treatment for the intervention group comprised three sets with 10 repetitions of pain-relieving glides delivered manually while the participant was performing the painful movement. For the sham group, the same procedure was mimicked for determining the pain-reducing glide direction without the glide force. A hand placement mimicking the pain-reducing glide was used for treatment. The dosage for repetitions in the sham group was same as in intervention group

FIGURE 2 Medial rotational glide of tibia in weight bearing

without the glide force. All the participants received standard therapy after completion of the study procedures.

2.5 | Outcome measures

The blinded outcome assessor recorded the outcome measures (NPRS and TUG) in both groups immediately before and after intervention/-sham therapy.

Numerical pain rating scale: Participants were provided with an 11-point numerical scale numbered from 0 to 10 and were explained that "0" meant no pain at all and "10" meant worst possible pain imaginable (McCaffery & Beebe, 1994). The participants marked an appropriate number on the scale, which accurately represented the average intensity of pain experienced during the knee movement.

Timed up and go test: It is an Osteoarthritis Research Society International-recommended performance measure to be used in interventional trials on patients with knee OA (Dobson et al., 2013). The intra and inter-rater reliability of this test was found to be excellent, with the intraclass correlation coefficients being 0.97 and 0.96; the minimal detectable change (MDC) was reported as 1.10–1.14 seconds in Grade 1–3 knee OA (Alghadir, Anwer, & Brismée, 2015).

The participants sat in a chair comfortably, facing a corridor, and a cone was placed at 3-m distance. Initially, the test was explained and demonstrated by the outcome assessor to the participants. The participant was instructed to get up from the chair on the assessor's call "go," walk for 3 meters, turn around, come back, and sit on the chair at a comfortable pace. The time is taken (in seconds) between the participant getting up from the chair and until they sat back on the chair was recorded by the assessor.

2.6 | Statistical methods

Statistical Package for the Social Sciences version 16.0 was used for data analysis. Descriptive statistics were used to report demographic data and to summarize the measures of central tendencies and dispersion for the outcome measures. The data were tested for normality using the Shapiro Wilk test and were found to follow a skewed distribution. Hence the non-parametric tests, that is, Kruskal Wallis H test was performed for between-group differences, and the Wilcoxon signed-rank test was performed for within-group differences.

3 | RESULTS

Among the 61 screened participants, 31 were excluded for reasons represented in the Consolidated Standards of Reporting Trials diagram (Figure 3). Both the intervention and sham groups had an equal number of participants (n = 15), and all recruited participants completed the study. One participant in the sham group received the intervention in the non-weight bearing position, and the remaining participants in both the groups were treated in the weight-bearing position. Table 1 summarizes the baseline demographics and descriptive statistics of the participants. In the intervention group, five participants were treated with medial rotational glides, and seven were treated with medial translational glides and three were treated with lateral translational glides.

The baseline pain scores were higher in the sham group than the intervention group. The Kruskal Wallis H test determined a statistically significant difference between the post-intervention scores of NPRS [$H(1) = 5.110$, $p = .024$] and the TUG [$H(1) = 7.155$, $p = .007$] with the intervention group demonstrating superior outcomes (Table 2). The effect sizes were reported in Table 2.

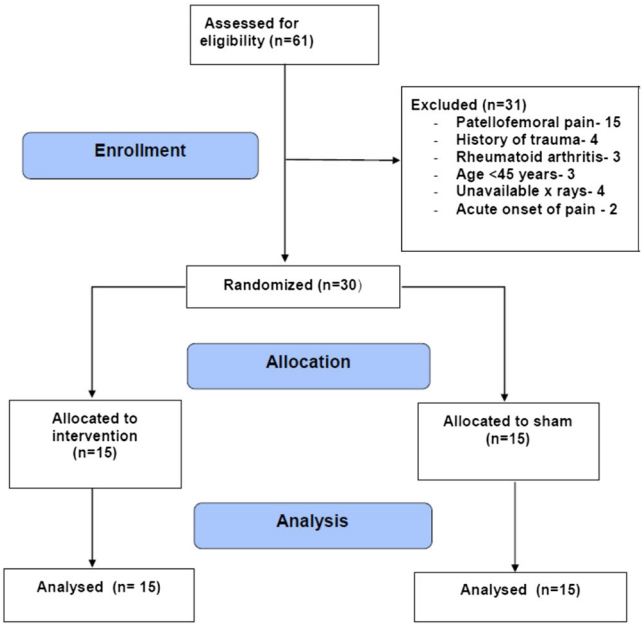

FIGURE 3 Consolidated Standards Of Reporting Trials flow diagram

TABLE 1 Baseline demographics (n = 30)

Demographics	Intervention	Sham
Age (mean ± *SD*) years	53.73 ± 7.06	56.87 ± 9.35
Side involved (Right: Left)	11:4	6:9
Male:female ratio	5:10	5:10
Grades of knee osteoarthritis		
I	4	8
II	11	5
III	0	2
Offending Movement		
Flexion	6	7
Extension	9	8
Pre-NPRS (median and IQR)	5.00 (4.00–7.00)	8.00 (5.00–8.00)
Pre-TUG (median and IQR)	11.67 (9.65–12.59)	12.86 (10.83–15.2)

Abbreviations: IQR, interquartile range; NPRS, numerical pain rating scale; *SD*, standard deviation; TUG, timed up and go test.

TABLE 2 Comparison of post-intervention outcome measures for the difference between the groups

	Groups (median and IQR)			
Outcomes	**Intervention**	**Sham**	***P* values**	**Effect size**
Post-NPRS	4.00 (2.00–5.00)	6.00 (4.00–7.00)	0.024	0.41
Post-TUG	10.9 (9.43–10.45)	13.18 (10.38–16.00)	0.007	0.49

Abbreviations: IQR, interquartile range; NPRS, numerical pain rating scale; TUG, timed up and go test.

The Wilcoxon signed-rank test for within-group differences revealed that the post-intervention scores of NPRS and TUG were significantly lower compared to the pre-intervention scores ($Z = -3.198$ and $p = .001$ and $Z = -2.244$ and $p = .025$, respectively) in the intervention group.

In the sham group, there was a statistically significant improvement in the post-NPRS scores as compared to the pre-NPRS ($Z = -2.980$, $p = .003$). However, there was no substantial change in the post-TUG scores when compared with the pre-TUG scores ($Z = -0.795$, $p = .427$) (Table 3).

4 | DISCUSSION

The current study investigated the immediate effects of Mulligan's techniques in comparison with sham therapy and identified that individually tailored Mulligan's MWM demonstrated a positive effect on knee pain and functional mobility in knee OA participants. No adverse events were reported after the treatment procedures in both groups.

The mechanisms for the pain-relieving effects of manual therapy techniques were categorized under three headings: biomechanical, neurophysiological, and non-specific mechanisms (Bialosky et al., 2009; Bishop, M.D et al., 2015). The biomechanical mechanisms in the context of Mulligan's technique could be the correction of positional faults by the treatment glides used in the intervention group of the present study. The passive Mulligan's techniques could have transiently restored the normal kinematics of the osteoarthritic knees producing immediate pain relief. The immediate effects after the intervention might also be attributed to the neurophysiological mechanisms that include the modulation of pain at spinal level (pain gate mechanisms; Neelapala, Reddy, & Danait, 2016), peripheral level (dispersal of inflammatory mediators), and supraspinal level (Malisza et al., 2003). The role of repeated movements of the knee during the mobilization techniques in pain relief should be considered in both the groups (Zusman, 2004).

The results of the current study demonstrated pain reduction in the sham group as well. The improvements in pain noticed in the sham group of our study might be due to the non-specific effects of pain modulation by manual therapy. The non-specific mechanisms include patient and provider expectations and addressing psychological factors such as fear, catastrophizing, kinesiophobia, and so forth. (Bialosky, Bishop, George, & Robinson, 2011). The sham induced hypoalgesia was shown to be possible, solely as a result of patient expectations and conditioning (Verne, Robinson, Vase, & Price, 2003). Besides, placebo or sham effects are attributed to activation of low threshold mechanoreceptors by the tactile input (McGlone, Wessberg, & Olausson, 2014).

In addition to the above reasons, the baseline NPRS scores of two participants in the sham group were high (8 and 10) and reduced by 4 and 5 scale points after the intervention respectively. Probably, such large magnitudes of pre–post changes in these two participants might also be responsible for the overall lower post-intervention mean pain scores in the sham group. However, the number of participants achieving MCID in pain scores (2 scale points on NPRS) were more ($n = 11$) in the intervention group than the sham group ($n = 7$).

Post-treatment, the participants in the intervention group performed better on timed up and go test when compared to the sham group. Four participants in the intervention group and five in the sham group demonstrated MDC in improvements on TUG scores. However, in the sham group, few participants ($n = 3$) required more time (more than MDC) post-treatment on TUG, and such deterioration was not observed in the participants of the intervention group. Overall, the timed up and go scores worsened in the sham group despite improvements in pain post-intervention.

There were no precisely equivalent previous studies on Mulligan's techniques to compare with our results. However, similar results were reported with the Mulligan's squeeze technique when compared with sham therapy in participants with medial meniscal tear (Hudson et al., 2018). Another study by Hanada et al., 2018 demonstrated that a single session of leg press exercise with the tibia in internal rotation

TABLE 3 Comparison of outcome measures within the groups

	Groups (median and IQR)					
	Intervention			**Sham**		
Outcomes	**Pre**	**Post**	***P* value**	**Pre**	**Post**	***P* value**
NPRS	5.00 (4.00–7.00)	4.00 (2.00–5.00)	0.001	8.00 (5.00–8.00)	6.00 (4.00–7.00)	0.003
TUG	11.67 (9.65–12.59)	10.9 (9.43–12.45)	0.025	12.86 (10.83–15.2)	13.18 (10.38–16.00)	0.427

Abbreviations: IQR, interquartile range; NPRS, numerical pain rating scale; TUG, timed up and go test.

position produced significant improvements in knee symptoms and function. Mulligan's MWMs and Maitland techniques (Rao *et al*., 2018) were found to be similar in improving pain, function, and a pain-free range of motion in knee OA. As the present study demonstrated identical improvements in knee pain among the groups, together, these findings may suggest a role of tactile input during manual mobilization techniques to some extent.

4.1 | Strengths and limitations

Joint mobilization techniques are frequently administered for knee OA individuals. The current study is the first to compare the effectiveness of isolated Mulligan's MWM with sham intervention. Such a comparison with sham techniques enabled to differentiate the specific biomechanical effects of Mulligan's techniques from the non-specific mechanisms as proof of the concept. As the study is a single session pre–post design, there is no influence of any other therapeutics (such as pharmaceutical agents). However, the study has the following limitations: (a) The study included individuals with bilateral knee OA, and the knee with higher pain score was intervened. But, the influence of contralateral knee pain on the functional outcome measure (TUG) could not be determined as the intensity of pain in the other extremity was not recorded at baseline (b) The sample size of the study is less, and only the immediate effects of Mulligan's techniques were investigated. As the treatment effects were compared with a sham group, a higher number of sham intervention sessions and a long-term follow-up were considered not ethical. As the current study intended to examine the isolated effects (as a proof of the concept), restricting the treatment groups solely to Mulligan's mobilization has ethical constraints. Therefore, it was decided to as *a priori* to investigate only the immediate effects of Mulligan's mobilization in comparison with shams.

4.2 | Future recommendations

As knee OA is a chronic condition, large-sized studies investigating the long-term effects of Mulligan's mobilization techniques with adequate follow-up are required. Future studies may attempt to quantitatively assess the biomechanical correction of positional faults due to Mulligan's techniques, and also, the mechanisms resulting in sham effects need to be ascertained further.

5 | CONCLUSION

Mulligan's techniques produced immediate effects in reducing knee pain and improving functional mobility in knee OA as compared with a sham intervention. In addition to the directional forces causing the correction of positional faults, the study provides preliminary support for non-specific mechanisms of pain relief of Mulligan's techniques due to the hypoalgesic effects identified in the sham group.

5.1 | Implications for physiotherapy practice

The results of the study showed that Mulligan's techniques are effective in proving immediate pain relief in individuals with knee OA. However, sham mobilization also produced pain reduction highlighting the role of touch and tactile input for achieving hypoalgesia during joint mobilization. Therefore, Mulligan's mobilizations can be used an effective short-term pain-relieving treatment option in patients with knee OA.

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NA

CONFLICT OF INTEREST

The authors report no conflict of interest.

FUNDING INFORMATION

None.

ETHICAL APPROVAL

The Institutional Ethics Committee, Kasturba Hospital, Manipal, India approved the study. The trial was registered with the Clinical Trial Registry of India with the reference number CTRI/2017/03/008073. Participant recruitment happened between July 2017–February 2018.

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REFERENCES

Alghadir, A., Anwer, S., & Brismée, J. M. (2015). The reliability and minimal detectable change of Timed Up and Go test in individuals with grade 1–3 knee osteoarthritis. *BMC Musculoskeletal Disorders*, *16*(1), 174. https://doi.org/10.1186/s12891-015-0637-8

Baker, R. T., Nasypany, A., Seegmiller, J. G., & Baker, J. G. (2013). The Mulligan concept: mobilizations with movement. *International Journal of Athletic Therapy and Training*, *18*(1), 30–34. https://doi.org/10.1123/ijatt.18.1.30

Bialosky, J. E., Bishop, M. D., George, S. Z., & Robinson, M. E. (2011). Placebo response to manual therapy: Something out of nothing? *The Journal of Manual & Manipulative Therapy*, *19*(1), 11–19. https://doi.org/10.1179/2042618610Y.0000000001

Bialosky, J. E., Bishop, M. D., Price, D. D., Robinson, M. E., & George, S. Z. (2009). The mechanisms of manual therapy in the treatment of musculoskeletal pain: A comprehensive model. *Manual Therapy*, *14*(5), 531–538. https://doi.org/10.1016/j.math.2008.09.001

Bijlsma, J. W., Berenbaum, F., & Lafeber, F. P. (2011). Osteoarthritis: An update with relevance for clinical practice. *The Lancet*, *377*(9783), 2115–2126. https://doi.org/10.1016/S0140-6736(11)60243-2

Bishop, M. D., Torres-Cueco, R., Gay, C. W., Lluch-Girbés, E., Beneciuk, J. M., & Bialosky, J. E. (2015). What effect can manual therapy have on a patient's pain experience? *Pain Management*, *5*(6), 455–464. https://doi.org/10.2217/pmt.15.39

Chiarotto, A., Ostelo, R. W., Turk, D. C., Buchbinder, R., & Boers, M. (2017). Core outcome sets for research and clinical practice. *Brazilian Journal of Physical Therapy*, *21*(2), 77–84. https://doi.org/10.1016/j.bjpt.2017.03.001

Cross, M., Smith, E., Hoy, D., Nolte, S., Ackerman, I., Fransen, M., … Laslett, L. L. (2014). The global burden of hip and knee osteoarthritis: Estimates from the Global Burden of Disease 2010 study. *Annals of the Rheumatic Diseases*, *73*(7), 1323–1330. https://doi.org/10.1136/annrheumdis-2013-204763

Dobson, F., Hinman, R. S., Roos, E. M., Abbott, J. H., Stratford, P., Davis, A. M., … Hansen, P. (2013). OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. *Osteoarthritis and Cartilage*, *21*(8), 1042–1052. https://doi.org/10.1016/j.joca.2013.05.002

Farrar, J. T., Young, J. P. Jr., LaMoreaux, L., Werth, J. L., & Poole, R. M. (2001). Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*, *94*(2), 149–158. https://doi.org/10.1016/S0304-3959(01)00349-9

Fernandes, L., Hagen, K. B., Bijlsma, J. W., Andreassen, O., Christensen, P., Conaghan, P. G., … Lohmander, L. S. (2013). EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Annals of the Rheumatic Diseases*, *72*(7), 1125–1135. https://doi.org/10.1136/annrheumdis-2012-202745

French, H. P., Brennan, A., White, B., & Cusack, T. (2011). Manual therapy for osteoarthritis of the hip or knee—A systematic review. *Manual Therapy*, *16*(2), 109–117. https://doi.org/10.1016/j.math.2010.10.011

Haahr, M. (2012). Random.org-Random Integer Generator. *Retrieved from* https://www.random.org/

Hamai, S., Moro-oka, T. A., Miura, H., Shimoto, T., Higaki, H., Fregly, B. J., … Banks, S. A. (2009). Knee kinematics in medial osteoarthritis during in vivo weight-bearing activities. *Journal of Orthopaedic Research*, *27*(12), 1555–1561. https://doi.org/10.1002/jor.20928

Hanada, K., Hara, M., Hirakawa, Y., Hoshi, K., Ito, K., & Gamada, K. (2018). Immediate effects of leg-press exercises with tibial internal rotation on individuals with medial knee osteoarthritis. *Physiotherapy Research International*, *23*(4), e1725. https://doi.org/10.1002/pri.1725

Hancock, M. J., Maher, C. G., Latimer, J., & McAuley, J. H. (2006). Selecting an appropriate placebo for a trial of spinal manipulative therapy. *The Australian Journal of Physiotherapy*, *52*(2), 135–138. https://doi.org/10.1016/S0004-9514(06)70049-6

Hochberg, M. C., Altman, R. D., April, K. T., Benkhalti, M., Guyatt, G., McGowan, J., … Tugwell, P. (2012). American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care & Research*, *64*(4), 465–474. https://doi.org/10.1002/acr.21596

Hudson, R., Richmond, A., Sanchez, B., Stevenson, V., Baker, R. T., May, J., … Reordan, D. (2018). Innovative treatment of clinically diagnosed meniscal tears: A randomized sham-controlled trial of the Mulligan concept "squeeze" technique. *The Journal of Manual & Manipulative Therapy*, *26*(5), 254–263.

Kaya Mutlu, E., Ercin, E., Razak Ozdıncler, A., & Ones, N. (2018). A comparison of two manual physical therapy approaches and electrotherapy modalities for patients with knee osteoarthritis: A randomized three arm clinical trial. *Physiotherapy Theory and Practice*, *34*(8), 600–612. https://doi.org/10.1080/09593985.2018.1423591

Kellgren, J. H., & Lawrence, J. S. (1957). Radiological assessment of osteo-arthrosis. *Annals of the Rheumatic Diseases*, *16*(4), 494–502. https://doi.org/10.1136/ard.16.4.494

Malisza, K. L., Stroman, P. W., Turner, A., Gregorash, L., Foniok, T., & Wright, A. (2003). Functional MRI of the rat lumbar spinal cord involving painful stimulation and the effect of peripheral joint mobilization. *Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine*, *18*(2), 152–159. https://doi.org/10.1002/jmri.10339

McCaffery, M., & Beebe, A. (1994). *Pain: Clinical manual for nursing practice*. London: Times Mirror International Publishers Limited.

McGlone, F., Wessberg, J., & Olausson, H. (2014). Discriminative and affective touch: Sensing and feeling. *Neuron*, *82*(4), 737–755. https://doi.org/10.1016/j.neuron.2014.05.001

Moro-oka, T. A., Hamai, S., Miura, H., Shimoto, T., Higaki, H., Fregly, B. J., … Banks, S. A. (2008). Dynamic activity dependence of in vivo normal knee kinematics. *Journal of Orthopaedic Research*, *26*(4), 428–434. https://doi.org/10.1002/jor.20488

Mulligan, B. R. (1993). Manual therapy rounds. *The Journal of Manual & Manipulative Therapy*, *1*(4), 154–156. https://doi.org/10.1179/jmt.1993.1.4.154

Neelapala, Y. V. R., Reddy, Y. R. S., & Danait, R. (2016). Effect of Mulligan's posterolateral glide on shoulder rotator strength, scapular upward rotation in shoulder pain subjects—A randomized controlled trial. *Journal of Musculoskeletal Research*, *19*(03), 1650014.

Paungmali, A., O'Leary, S., Souvlis, T., & Vicenzino, B. (2004). Naloxone fails to antagonize initial hypoalgesic effect of a manual therapy treatment for lateral epicondylalgia. *Journal of Manipulative and Physiological Therapeutics*, *27*(3), 180–185. https://doi.org/10.1016/j.jmpt.2003.12.022

Qinguang Xu, M. D., Bei Chen, M. D., Yueyi Wang, M. D., Xuezong Wang, M. D., & Dapeng Han, M. D. (2017). The effectiveness of manual therapy for relieving pain, stiffness, and dysfunction in knee osteoarthritis: A systematic review and meta-analysis. *Pain Physician*, *20*, 229–243.

Rao, R. V., Balthillaya, G., Prabhu, A., & Kamath, A. (2018). Immediate effects of Maitland Mobilization versus Mulligan Mobilization with Movement in osteoarthritis knee—A randomized crossover trial. *Journal of Bodywork and Movement Therapies*, *22*(3), 572–579. https://doi.org/10.1016/j.jbmt.2017.09.017

Ribeiro, D. C., de Castro, M. P., Sole, G., & Vicenzino, B. (2016). The initial effects of a sustained glenohumeral postero-lateral glide during elevation on shoulder muscle activity: A repeated measures study on asymptomatic shoulders. *Manual Therapy*, *22*, 101–108. https://doi.org/10.1016/j.math.2015.10.014

Saari, T., Carlsson, L., Karlsson, J., & Kärrholm, J. (2005). Knee kinematics in medial arthrosis. Dynamic radiostereometry during active extension and weight-bearing. *Journal of Biomechanics*, *38*(2), 285–292. https://doi.org/10.1016/j.jbiomech.2004.02.009

Takasaki, H., Hall, T., & Jull, G. (2013). Immediate and short-term effects of Mulligan's mobilization with movement on knee pain and disability associated with knee osteoarthritis—A prospective case series. *Physiotherapy Theory and Practice*, *29*(2), 87–95. https://doi.org/10.3109/09593985.2012.702854

Verne, G. N., Robinson, M. E., Vase, L., & Price, D. D. (2003). Reversal of visceral and cutaneous hyperalgesia by local rectal anaesthesia in irritable bowel syndrome (IBS) patients. *Pain*, *105*(1-2), 223–230.

Zusman, M. (2004). Mechanisms of musculoskeletal physiotherapy. *Physical Therapy Reviews*, *9*(1), 39–49. https://doi.org/10.1179/108331904225003973

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