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Osteoarthritis (T Appleton, Section Editor)

Why Is Exercise Effective in Reducing Pain in People with Osteoarthritis?

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Abstract

Purpose of the review The aim of this narrative review was to summarize the beneficial effects of exercise for those with symptomatic hip and knee osteoarthritis (OA) utilizing data along the pipeline from translational to clinical studies to implementation into clinical practice.
Recent findings Exercise is first line treatment for managing symptomatic hip and knee OA. Aerobic, strengthening and neuromuscular approaches are all effective in reducing pain and improving function. Exercise dose and supervision may be more important. Twelve or more supervised exercise sessions seem superior to fewer sessions. Education about the condition, the role of exercise in reducing pain and improving function, and strategies for increasing physical activity is also key as long-term adherence to ongoing home exercise after program attendance is needed to maintain effects. The proposed mechanisms by

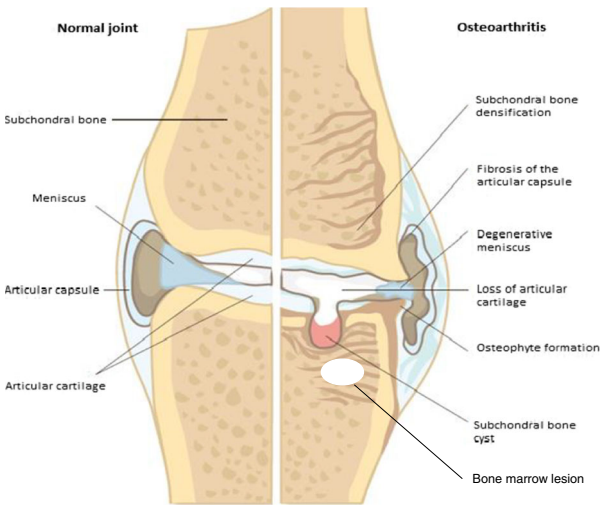
which exercise improves pain and function in people with OA include general systemic effects and those local to the joint. General mechanisms include neural and systemic inflammation effects. Local mechanisms include exercise effects on muscle and other joint-related structures as well as local joint inflammation. Exercise effects on pain are as large or larger than for medications such as paracetamol and NSAIDs. Similar magnitude in pain relief and improvement in function from clinical trials has been shown immediately after the program and at 1-year follow-up in evidence-based structured education and exercise programs implemented into clinical practice in several countries. These programs are cost-effective.

Summary Although clinicians around the world are slowly adopting exercise as OA treatment, system changes are required to facilitate implementation of evidence-based exercise programs into clinical practice. Enhanced availability of education and supervised exercise programs and reimbursement schemes with support from publicly funded health services that reduce access barriers for patients are needed to support more universal evidence-based management and reduce the burden of symptomatic OA.

Introduction

Symptomatic osteoarthritis (OA) affects approximately 10% of people, and the World Health Organization estimates that 18.0% of women and 9.6% of men 60 years of age and over have symptomatic OA [1]. The hip and knee are the most commonly affected joints. Pain is a hallmark of OA that limits function, mobility, work productivity, and physical activity, and reduces health-related quality of life (HRQOL) [2]. Thus, OA is an overwhelming personal and societal burden.

OA affects all joint structures (Fig. 1), and biomechanical and inflammatory components are implicated in OA genesis and progression [3]. OA is challenging to define and treat because symptoms and structural changes in the joint are not well correlated. OA is recognized as a disease that involves the whole person. People's response to pain, the functional limitations they experience, and their response to interventions are impacted by biopsychosocial factors as well as their general and joint health [4]. Additionally, two-thirds of



Pains and sensitivities in osteoarthritis (OA)
- nociceptive pain
- neuropathic pain

Location of nociceptors in the joint affected in OA
- joint capsule
- ligaments
- menisci periphery
- periosteum
- subchondral bone
- muscle
- tendon

Fig. 1. Joint structures with osteoarthritic changes.

people with OA have other chronic conditions such as diabetes and cardiovascular disease, many of which are associated with low-grade systemic inflammation [5].

Evidence-based guidelines for the first-line treatment of hip and knee OA consistently support exercise, education, and weight management for those with symptomatic OA [6••, 7]. In this review, we provide an overview of the evidence that highlights that exercise is beneficial for those with OA. The evidence comes from data along the pipeline from translational to clinical studies to implementation into clinical practice. While we recognize that biopsychosocial factors and weight loss have an impact on the OA experience and pathogenesis (e.g., as little as 5% weight loss is effective in reducing symptoms [8]), we focus on exercise as treatment. Specifically, we focus on exercise for hip and knee OA as there are limited data on exercise for generalized OA and other individual joints. The review of the inflammatory and mechanical aspects of OA provides background for presenting the relationship of exercise with these aspects of OA which may in turn be associated with improvements in pain and function. We then describe the implementation of the current evidence into clinical practice for management of symptomatic hip and knee OA in several countries.

Setting the stage: impaired mechanics and inflammation in OA

OA is a complex disease involving mechanical stress, biochemical, and biological processes that affect the entire joint and surrounding muscles. Figure 1 shows the structures of the knee joint affected by OA. Joint trauma is common, especially in young adults, and injuries to the ligaments and menisci are often associated with cartilage damage and bone marrow lesions, predisposing to OA in about 50% of people followed 10 years or more [9]. Injury to multiple joint structures also increases OA risk [9]. Excessive, prolonged loading or abnormal/poorly distributed load and mechanical stress result in loss of hyaline cartilage [10]. Conversely, immobilization or too little loading results in cartilage thinning [11]. Degenerative meniscal tears are common [12]. Reactive bone processes occur [13], such as the development of osteophytes, which are thought to stabilize the altered joint [14]. There is increased stiffness of the subchondral bone and bone marrow lesions are common. Additionally, many hallmarks of inflammatory diseases, soluble inflammatory mediators such as cytokines (e.g., TNF-alpha, IL-1, IL-6, IL-10, IL-15), chemokines (e.g., MCP-1 fractalkine), and adipokines and their role in OA pathogenesis have been identified [15–18] as has mild to severe synovitis [19, 20]. Obesity is associated with OA through both excess mechanical load [21] and through inflammatory and metabolic mechanisms as fat is an endocrine organ secreting multiple pro-inflammatory mediators [22] which are associated with systemic low-grade inflammation implicated in damage to peripheral structures including joints [15].

Muscle weakness is a risk factor for OA [23] but also may result from OA. A review by Alnahdi et al. concluded that people with knee OA had quadriceps strength deficits ranging from 10 to 56% compared with healthy controls during isokinetic testing with even greater deficits during eccentric testing [24]. Strength deficits result from muscle atrophy and weakness results from sensorimotor deficiency [24–26]. The altered sensorimotor response is mediated by pain and inflammation. Inflammation often results in swelling which can damage sensory receptors in the joint. The excitability of spinal and supraspinal pathways are altered with failure to recruit all motor units, reduction in motor unit firing rate, and incomplete activation of the muscle [24–26]. This results in decreased strength but also abnormal muscle activation patterns, lack of coordinated timing of muscle contraction during functional activity, reduced dynamic joint stability, impaired postural control, and physical performance, all of which increase the joint load during functional activities.

Pietrosimone et al. conducted a systematic review of volitional quadriceps activity in people with knee OA and found that there was an activation deficit bilaterally in those with OA compared with healthy controls. This deficit was more pronounced in the involved limb [27]. Additionally, work by Fisher et al. showed that force development and endurance were 60% and 33%, respectively, in those with knee OA compared with healthy controls [28].

First-line treatment for OA: defining exercise

Exercise and physical activity are terms used interchangeably in the literature despite having specific meaning. Physical activity is any bodily movement produced by skeletal muscles that results in energy expenditure. Exercise is a subset of physical activity that is planned, structured, and repetitive with the objective of improvement or maintenance of physical fitness [29]. Exercise therapy is a subset of exercise with specific therapeutic aims [30]. Studies for OA largely reflect exercise therapy although we use "exercise" throughout this paper.

Types of exercise include aerobic, strengthening, and neuromuscular exercise. Aerobic exercise targets improved cardiovascular fitness. Strengthening tends to

be non-weight bearing and focused on a single muscle group, whereas neuromuscular exercise focuses on weight-bearing functional activities with attention to limb alignment and motor control. While exercise is effective in reducing pain and improving function [6••, 7, 31], there is insufficient evidence to recommend one type or a combination of exercise types as superior; nor is there conclusive evidence to support a specific exercise dose for pain relief [32]. However, at least 12 supervised sessions seem superior to fewer sessions in people with knee OA [31, 33]. Pain relief from exercise was similar in those with knee OA irrespective of radiographic stage and pain severity [31].

How effective is exercise in improving pain and function?

More than 50 randomized trials show the positive effect of exercise in relieving pain and improving function in people with symptomatic hip or knee OA [31, 34–36]. The effect sizes (ES) for people with symptomatic knee OA are 0.49 and 0.52 for pain and function, respectively, and 0.38 for both pain and function in people with symptomatic hip OA [34, 35]. These effects are larger than for non-steroidal anti-inflammatory medications. Based on a meta-analysis of randomized controlled trials, NSAIDs had an ES ranging from 0.17 to 0.35 (knee 0.32 and 0.35 for pain and function, respectively; hip 0.26 and 0.17 for pain and function, respectively) [6••]. Exercise resulted in mean absolute improvement in pain and function respectively of 12 points; (95% CI 10–15) and 10 points; (95% CI 8–13) for those with knee OA [34]. In those with hip OA, exercise reduced pain and function respectively by an average of 8 points (95% CI 4–11) and 7 points (95% CI 1–12) [35]. These reviews used validated pain measures with a score range of 0–100.

Exercise and possible mechanisms for improving pain and function

Runhaar et al. explored the possible mechanism by which exercise reduces pain and improves function [37]. They conducted a systematic review of randomized trials of exercise in people with knee OA that focused on secondary physiological outcomes. Outcomes were grouped in broad categories: strength, proprioception, inflammation, gait properties, muscle properties, cartilage OA properties, range of motion/flexibility, biomechanics, body weight/metabolic syndrome, bone properties, joint stability/balance, and aerobic capacity. The results indicated that only quadriceps and hamstring strength, knee extension impairments, and proprioception were potential mediators of exercise with pain and function. The authors noted that there were inconsistent outcomes across studies and that the studies were underpowered to detect a change in the secondary outcomes, limiting the interpretation of the results. Additionally, broad categorization of the outcomes may mask the results of individual physiologic outcomes. Hence, there remains a need for appropriately powered studies to identify potential mechanisms related to the mechanical and inflammatory aspects of OA that might be associated with improved pain and function from exercise. While exercise prescription is directed to improving pain and function in those with OA, understanding how this first-line therapy impacts the inflammatory and mechanical aspects of OA may also aid in understanding and interpreting the results of multi-modal interventions with an opportunity to enhance therapeutic effects and improve outcomes for people with symptomatic OA.

Pain and neural mechanisms

As shown in Fig. 1, nociceptors are abundant in the joint structures affected in the OA process. Pain is commonly associated with OA and manifests both as ongoing pain at rest as well as pain evoked by normally non-painful movements and other stimuli (allodynia, hyperalgesia). The pain experience also is affected by psychosocial factors [38].

It is important to recognize some fundamental elements of the pain system to understand the neural mechanisms underlying pain. The International Association For the Study of Pain (IASP) defines pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [39]. In contrast, the IASP defines nociception as "The neural process of encoding noxious stimuli" [39]. These definitions highlight the important difference between pain and nociception, with pain being a subjective experience that is thus only truly known through self-report, whereas nociception refers to how the peripheral and central nervous system responds to noxious stimuli. This distinction is also important because there are advancing developments in the use of brain imaging to understand pain but also in the quest for an objective measure of a fundamentally subjective experience [40•].

The neural mechanisms underlying joint pain in general and pain in OA involve both peripheral and central elements. The central mechanisms of joint pain and pain in OA share some key features with other pains [41, 42]. In general, activation of primary afferent nociceptors that innervate skin, joints, muscles, and viscera results in activation of nociceptive neurons in the spinal dorsal horn and signals are then transmitted to various

areas of the thalamus, brainstem, and cortex. These activities also trigger descending signals from regions in the brain/brainstem associated with pain modulation. Joint and other deep afferents mostly converge onto neurons that also receive information from the skin, that shape characteristic patterns of referred pains. Traditionally, pain was thought to arise from activity along so-called nociceptive pathways (e.g., spinothalamic tract, thalamocortical tract, etc.). However, it is now recognized that the individual pain experience is shaped by the balance of activity along ascending nociceptive pathways and descending antinociceptive pathways [43]. Furthermore, the new concept of a "dynamic pain connectome" emphasizes that an individual's pain experience is being constantly shaped not only by these two pathways but additionally by the activity and connectivity in brain networks associated with salience, attention, and internal thoughts—i.e., salience, attention, and default mode networks [41]. There is a link between the engagement of the dynamic pain connectome and acute pain experiences, which can vary across individuals [44].

In OA and other chronic pains, there may also be peripheral and central sensitization in neuronal responses (e.g., in nociceptive neurons in the spinal dorsal horn, the thalamus, and cortex) that accounts for the behavioral phenomena such as allodynia and hyperalgesia [45]. Quantitative sensory testing of pain thresholds and suprathreshold responses to noxious and innocuous stimuli at/near the joint and at remote body areas can be used as a proxy indicator of peripheral and central sensitization. Such testing suggests that peripheral sensitization occurs in up to 30% of people with knee OA [46, 47]. Furthermore, the attention, salience, and default modes networks may be more or less engaged by the pain induced by OA. Treatments that reduce OA-related pain, such as exercise, may work directly or indirectly to alter activity in these networks and the other pathways of the dynamic pain connectome.

Various endogenous systems, neurotransmitters, receptors, and enzymes may be involved in exercise-induced analgesia. As reviewed by da Silva Santos et al. [48•] and Rice et al. [49•] various endogenous systems are activated during and after exercise. Substances and neurotransmitters, such as opioids, serotonin, nitric oxide, endocannabinoids, and catecholamines are released that may modulate people's pain perception [48, 49].

Joint structures and inflammation

Research has shown that exercise may positively impact some of the joint structures, most specifically muscle and articular cartilage in those with OA.

Muscle

Muscle strength

Muscle weakness and altered neuromuscular control are hallmarks of symptomatic OA, and studies show that strengthening exercises positively impact muscle structure and improve muscle strength. A recent systematic review of randomized trials by Liao et al. showed that muscle strengthening exercises increased muscle mass (standardized mean difference (SMD) 0.49 (95% CI 0.28, 0.71) and cross-sectional area (SMD 0.82; 95% CI 0.20, 1.43) in older adults with symptomatic knee OA compared with non-exercises controls [50••]. Subgroup analyses suggest that the effect is larger in men than for women. Resistance training exercise, irrespective of the type of training, resulted in increased muscle strength. Lange et al. reported a 17.4% increase in muscle (quadriceps) strength (ES 0.38) [51]. These improvements occurred in patients who were painful when starting to exercise, supporting that achieving improved muscle strength is possible despite having joint-related pain.

While much of the literature has focused on the knee extensors in those with knee OA, others have evaluated the hip muscles as these also seem to be weak in people with knee OA [52]. Chang et al. conducted a 12-week hip abductor strengthening program and participants achieved improved hip abductor strength [53]. Work by Bennell et al. supports these findings [54].

Recent work by Hernandez et al. also identified the potential importance of core strengthening in those with lower extremity OA [55]. The core, which consists of the abdominal, paraspinal, gluteal, pelvic floor, and hip girdle muscles, controls the trunk and pelvic position and movement so as to allow optimized transfer and control of forces generated in the distal segments of the lower limb. In a small randomized trial of people with knee OA, people who completed an exercise program inclusive of standardized strengthening and stretching exercises as well as core strengthening had a significant earlier improvement in knee pain compared with those in the control group performing only standardized exercises. While not statistically significant, the intervention group also had an improved number of chair stands which reflects strength, as well as improved walking speed and improved self-reported function [55].

Neuromuscular control

Strengthening protocols typically involve non-weight-bearing exercises and target an isolated muscle group. Given the abnormal motor patterns observed in people with OA of the hip or knee and that synchronized motor control is required for optimal functioning, isolated strengthening may be insufficient to optimally impact joint loading and daily functions such as stair climbing. Furthermore, it has been suggested that restoring mechanical constraints on a joint (i.e., by improving muscle strength and hence joint stability) is not sufficient for functional recovery [56]. Indeed, strength and neuromuscular activation predict disability in people with knee OA [27, 57].

Neuromuscular training stimulates both afferent signals and central mechanisms responsible for dynamic control with the goal of improving the neuromuscular system's generation of optimal muscle firing (activation of muscle fibers, rate of firing and synchronicity), all of which play a role in the generated muscle force [24] and dynamic joint stability. Neuromuscular exercise generally includes functional, weight-bearing exercises while maintaining a properly aligned lower limb (i.e., knee over foot position) that replicate situations in daily life and less frequent, more demanding activities that require dynamic joint stability. Examples include repeated stand from sitting and use of a step box replicating stepping up/down a stair. While all types of exercise are effective in relieving pain and improving function, it appears that neuromuscular training is superior to quadriceps strengthening for those with knee OA who are not obese but exhibit varus thrust [58].

Articular cartilage

Cartilage health is dependent on appropriate cyclic loading [10] and reduced loading results in thinning [11]. Excessive loading is a risk factor for OA but what is the effect of therapeutic exercise on cartilage? Overall, the literature seems to support that while exercise does not increase articular cartilage in people with established OA, moderate loading exercise is not detrimental to cartilage and may improve the health of existing cartilage.

A systematic review by Bricca et al. [59] found that loading exercise was not detrimental to cartilage as evaluated by MRI parameters in people with knee OA. Type of exercise varied and ranged from 1 to 5 times per week from 12 to 72 weeks. While limited to a narrative review due to study heterogeneity, between-group differences showed contradictory results. In the 2 studies of those at risk of OA, one in older women showed no effect on cartilage defects [60] while

the other in middle-aged individuals with meniscectomy showed increased glycosaminoglycan (GAG) content [61]. In the 12 studies of those with diagnosed OA, 6 comparisons showed no effect on cartilage thickness, volume, or defects [62–64]; 1 showed no effect on GAG [65]; 1 showed no effect on cartilage composition but there was a positive effect on collagen [66]; 1 showed a positive effect on collagen in the patellofemoral joint but not the tibiofemoral joint; and another showed no effect on collagen. For the exercise group, pre-post comparisons showed increased cartilage volume, increased GAG content and that there was a positive effect on cartilage defects. There was one negative result in these 14 within-group comparisons where there was decreased GAG content [66].

Cartilage and inflammatory biomarkers

Others also found that moderate exercise seems to be associated with a reduction in cartilage degradation and inflammation as evaluated by various biomarkers. Mazor reviewed human and animal studies and concluded that while weight-bearing exercise results in increases in cartilage degradation biomarkers such as cartilage oligomeric matrix protein (COMP), these increases are not different between those with OA and healthy controls, and the biomarkers return to normal relatively quickly after the therapeutic strengthening exercise [67]. COMP measured in serum returned to normal within 30 min of a 60-min exercise session and remained at normal levels 24 weeks later [68]. Isometric quadriceps exercise of 90 repetitions per day for 3 months showed a significant increase in hyaluronic acid in synovial fluid of OA patients compared with controls and there was a significant decrease in cartilage degradation markers C4S and C6S [69]. In another study, IL-10, which has an anti-inflammatory role, increased with quadriceps strengthening [70]. Helmark et al. additionally showed a decrease in synovial fluid COMP while there was no change from baseline in the cartilage degradation and inflammatory markers aggrecan, CTX-II and IL-6 after 30 min of exercise [71]. In a pilot trial, Hunt et al. evaluated biomarkers in patients with radiographically confirmed OA randomized to 10 weeks of physiotherapist-supervised hip abductor, quadriceps, and hamstring strengthening compared with no strengthening [72]. These authors found a significantly greater change in serum COMP in the exercise group compared with those in controls with the exercise group experiencing a decrease and the control experiencing an increase in COMP and CTS-II measured in urine. There was no change in urinary type II collagen cleavage neoepitope (uC2C), serum hyaluronic acid (sHA), or serum C-propeptide of type II procollagen (sCPII).

Bricca et al. also conducted a systematic review of cartilage and inflammatory biomarkers restricted to randomized trials of exercise in people at risk of or with knee OA compared to non-exercising control groups [73]. Overall, the quality of the evidence was low and while the authors could not definitively conclude positive effects of exercise on any biomarkers from their review, they did conclude that there were no detrimental effects of exercise on cartilage turnover or inflammatory biomarkers.

Systemic low-grade inflammation and exercise

The majority of people with OA have other comorbidities [5] many of which are associated with chronic low-grade inflammation e.g. cardiovascular disease, type 2 diabetes, dementia [74, 75]. Several reviews have identified that exercise is effective in preventing chronic conditions and in improving patient outcomes

in those with chronic conditions [75–77]. Reduction of low-grade inflammation has been suggested as a possible working mechanism by which exercise improves outcomes in people with chronic conditions [74, 75]. The impact of exercise on systemic inflammation in those with OA is less clear. A recent systematic review by Schulz et al. found that while IL-6 decreased in those with knee OA performing aerobic exercise compared to a non-exercise control, the effect was modest (0.37 pg/mL) and not statistically significant [78]. However, the results need to be interpreted with caution as there was a significant risk of bias in the three included studies and it appeared the exercise dose was sub-optimal for aerobic training.

In summary, while current evidence suggests that exercise may impact inflammation in those with OA, high quality sufficiently powered trials are required to understand the magnitude of effect and the potential dose-response relationship. Particular attention needs to be paid to differentiating the effect on local joint inflammatory biomarkers (usually from synovial fluid) and systemic biomarkers evaluated from blood serum or urine. Serum or urine markers generally reflect total body inflammation (i.e., from all involved joints and from other chronic conditions where inflammation is common). Such studies will enhance mechanistic understanding and have the potential to optimize and target exercise dose.

Implementation: translating exercise trial data into clinical practice

Several countries have implemented evidence-based education and exercise programs for people with symptomatic hip and knee OA [79]. Provision of patient education in addition to the exercise program facilitates understanding of the condition and that exercise is safe and can be conducted within acceptable and diminishing pain levels. This knowledge is critical for patients as pain on activity is a common complaint, yet as people exercise, pain flares and intensity are reduced [80]. Additionally, the importance of weight management and incorporation of general physical activity into daily life are addressed as part of the education.

Good Life with osteoArthritis in Denmark (GLA:D®) which includes 12 sessions of supervised, individualized exercises based on a neuromuscular approach delivered in a group setting is most widely implemented with programs in Denmark, Canada, Australia, China, Switzerland and New Zealand [81]. Results from the registries indicate pain and function improvements as good as or better than those reported in reviews of trials [34–36]. Based on data from the Danish, Canadian and Australian registries, within-group pain intensity reduced 25–33% on average with a 7–13% increase in walking speed and a 17–30% increase in number of chair stands in 30 s [82]. The demonstrated short-term improvements in pain and function is sustained at long-term follow-up [83, 84]. Other programs such as Better Management of Patients with Osteoarthritis (BOA) [85, 86] and Escape Pain [87•] have been successfully implemented in Sweden and the United Kingdom respectively. Importantly, the implementation of these programs also has demonstrated cost-effectiveness [88•] and cost savings [87•, 89•].

Conclusions

Osteoarthritis results in a significant burden to the individual and society. Inflammation and mechanical load are implicated in the genesis of OA and all structures of the joint are affected by OA. Many of the joint structures are rich

in nociceptors with pain and functional limitations and decreased quality of life hallmarks of the condition.

Exercise is a first-line therapy for managing OA symptoms and effectively reduces pain and improves function in those with knee and or hip OA. A minimum of twelve supervised exercise sessions seem to be most beneficial and neuromuscular approaches seem to be superior to strengthening alone in people with varus thrust of the knee who are not obese. Neural mechanisms, improved muscle strength and neuromuscular control, improved cartilage health, and reduced systemic and local joint inflammation may mediate the relationship of exercise with pain and functional outcomes. Most of the evidence reflects findings from those with knee OA and to a lesser extent with hip OA such that it is unclear if or to what extent these findings are generalizable to OA symptoms in other joints.

The magnitude of improvement in pain and function observed in randomized clinical trials is also observed in clinical practice. Education and evidence-based exercise programs are cost-effective and have been implemented successfully in a number of countries. Further implementation of such programs in other countries is critical to address the burden of symptomatic OA.

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Compliance with Ethical Standards

Conflict of Interest

Aileen M. Davis is a member of the Board of Osteoarthritis Research International (OARSI) and Associate Editor of Osteoarthritis and Cartilage. She is also on the Editorial Board of Arthritis Care and Research.

Karen D. Davis is the president of the Canadian Pain Society effective May 2020, and on the editorial boards of Pain Report, Pain, the Canadian Journal of Pain, and eNeuro. She is also a member of the Advisory Board of the Mayday Fund Fellows program, and the Institute of Neuroscience, Mental Health and Addiction of the Canadian Institutes of Health Research.

Soren T. Skou is an Associate Editor of the *Journal of Orthopaedic & Sports Physical Therapy* and has received grants from The Lundbeck Foundation, personal fees from Munksgaard, all of which are outside the submitted work. He is the co-founder of Good Life with Osteoarthritis in Denmark (GLA:D®), a not-for-profit initiative hosted at University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

Ewa M. Roos is a Deputy Editor of Osteoarthritis and Cartilage, the developer of the Knee Injury and Osteoarthritis Outcome Score (KOOS) and several other freely available patient-reported outcome measures and co-founder of GLA:D®.

Human and Animal Rights and Informed Consent

With regard to the authors' research cited in this paper, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee

and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In addition, all applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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