REVIEW

The pain-relieving qualities of exercise in knee osteoarthritis

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Abstract: The purpose of this review article is to explore the role of therapeutic exercise in managing the pain associated with knee osteoarthritis (OA). Therapeutic exercise is often recommended as a first-line conservative treatment for knee OA, and current evidence supports exercise as an effective pain-relieving intervention. We explore the current state of evidence for exercise as a pain-relieving intervention for knee OA. Next, the mechanisms by which knee OA pain occurs and the potential ways in which exercise may act on those mechanisms are discussed. Clinical applicability and future research directions are suggested. Although evidence demonstrates that exercise reduces knee OA pain, optimal exercise mode and dosage have not been determined. In addition, it is not clearly understood whether exercise provides pain relief via peripheral or central mechanisms or a combination of both. Published clinical trials have explored a variety of interventions, but these interventions have not been specifically designed to target pain pathways. Current evidence strongly supports exercise as a pain-relieving option for those with knee OA. Future research needs to illuminate the mechanisms by which exercise reduces the pain associated with knee OA and the development of therapeutic exercise interventions to specifically target these mechanisms.

Keywords: knee, OA, exercise, pain

Background

Knee osteoarthritis (OA) is the most common form of OA in the USA, with an estimated prevalence of symptomatic knee OA in 10%–16% of older adults in the USA according to the Centers for Disease Control and Prevention.[1,2] Prevalence of knee OA increases with age, ranging from 3% among those aged 45–54 years old to 44% in those at least 80 years old.[3] These prevalence estimates are expected to increase as the US population continues to age and obesity rates rise.[4]

Risk factors for knee OA include advancing age and previous history of trauma.[5] Familial clustering and twin studies have shown a probable genetic component for the development of knee OA, though environmental factors may also play a role in its development.[6,7] The presence of obesity has been shown to be associated with increased risk of knee OA, and may also increase the rate of articular cartilage degeneration.[8,9] The most commonly reported symptom of knee OA is pain, and pain has been identified as the top clinical concern for those with OA.[10] Overall, higher levels of pain from knee OA are linked to lower physical function and lower quality of life.[6] Thus, relief of pain is paramount in improving the lives of those with knee OA.

Conservative treatments for knee OA pain are numerous. More than half of those with knee OA report taking over-the-counter pain medications, while approximately

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one-third use vitamins or other dietary supplements and various topical ointments.[11] Physical modalities such as transcutaneous electrical nerve stimulation, laser, electroacupuncture, magnets, and therapeutic ultrasound have been studied with varying results.[12,13] The benefits of supplements such as glucosamine and chondroitin sulfate continue to be under investigation, with results as yet inconclusive.[14] Some with knee OA also attempt to manage pain with psychological interventions such as cognitive behavioral therapy and pain-coping skills training.[15,16] Injections of cortisone or hyaluronic acid are quite common. Despite myriad treatment options, one study found that 19% of those with knee OA report that their pain is not adequately controlled.[17]

Therapeutic exercise is often recommended as a first-line conservative treatment for knee OA. The American Academy of Orthopaedic Surgeons 2013 guidelines for the treatment of knee OA include a strong recommendation for strengthening, low-impact aerobic exercise, neuromuscular education, and physical activity for those with symptomatic OA,[18] while the American College of Rheumatology's 2012 recommendations for the management of knee OA include a strong recommendation for aerobic and/or resistance land-based exercise as well as aquatic exercise.[19] Similarly, the 2008 expert consensus guidelines from the Osteoarthritis Research Society International advocate regular aerobic, strengthening, and range-of-motion exercise for all patients with knee OA.[1]

The overall aim of this review is to explore the role of therapeutic exercise in managing pain associated with knee OA. Specifically, we first discuss current evidence supporting exercise as a pain-relieving intervention then the mechanisms of pain generation in knee OA are explored, and how exercise may act on these mechanisms to relieve knee OA pain. Finally, the clinical applicability of the current evidence and directions for future research are suggested.

Evidence supporting exercise as pain relieving

Despite increased public awareness of the importance of exercise and physical activity, only 27.8% of those with knee OA engage in regular moderate or vigorous physical activity.[20] The evidence base supporting exercise as a means to reduce pain in knee OA continues to grow.

Published in 2005, the MOVE consensus outlines recommendations for the use of exercise to manage hip and knee OA.[21] These recommendations promote both strengthening and aerobic exercise as a means to reduce OA pain, with the addition of behavioral interventions to promote long-term

lifestyle changes to maintain increased levels of physical activity. The authors also recommend that exercise therapy be individualized based on age and comorbidities, but group and home exercise are equally effective. Finally, the authors support the effectiveness of exercise in all stages of OA and state that exercise may reduce the progression of knee OA, although they acknowledge that these recommendations are based on expert opinion and are not supported by evidence in existence at the time of publication. Given the fairly generous number of effectiveness studies published since 2005 in the area of exercise for knee OA, these recommendations may be ripe for reassessment and updating.

Several recent reviews have been published regarding the strength of evidence supporting exercise as a pain-relieving intervention for those with knee OA.[15,22–26] Most have reported that exercise does indeed reduce pain, but effect sizes are small to moderate at best. Relatively small effect size, inadequate dosage, and lack of research comparing different modes of exercise are common limitations of the current evidence.

A 2009 Cochrane systematic review of 32 studies of land-based exercise for knee OA concluded that platinum-level evidence supports land-based therapeutic exercise for at least short-term pain reduction, but long-term effects are unclear and pooled effect sizes are small.[24] Unfortunately, this review did not consider the mode of intervention used – both aerobic and strengthening interventions were included, both weight-bearing (WB) and non-weight-bearing (NWB) interventions were included, and none of the authors' comparisons attempted to note whether any particular mode was most effective for pain relief. The review did conclude that studies that provided an individual intervention produced greater pain relief than class- or home-based interventions; however, no conclusions could be made regarding the most effective mode or dosage of exercise for knee OA pain.

Although modest effect sizes appear to be a common denominator among published studies of exercise for knee OA pain, the quality and dosage of the interventions provided are also limiting factors. In the aforementioned Cochrane review of land-based exercise for knee OA,[24] only 12 of the 32 studies included provided interventions at least twice per week for at least 8 weeks. Several focused on strengthening only one muscle group (the quadriceps femoris) or provided very elementary interventions such as education about exercise or simple range-of-motion exercises, which are unlikely to independently produce a training effect or significant pain relief. Many of the included studies involved home-based interventions with minimal supervision. The overall pooled

effect size for pain relief of the 32 studies was 0.40. Of the 12 studies that provided an intervention likely to produce an effect, only one had an effect size for pain relief below 0.40. Thus, it appears that mode, intensity, and frequency of intervention play a large role in pain relief.

Following, we explore the pain-relieving effects of various modes of exercise that have been studied, including the appropriate dosage to provide pain relief for those with knee OA.

Aerobic

Evidence appears to support aerobic exercise as effective for pain relief, but the current published research is lacking quality information on the optimal mode and dosage. Two recent studies noted pain relief following a community-based walking intervention[27] and following a group stationary cycling program.[28] However, the walking intervention study had a very large dropout rate at the follow-up period, and effect sizes for pain were small to moderate.[27] The stationary cycling study demonstrated moderate to large effect sizes for pain variables, but there was no follow-up beyond the end of the intervention period, so it is unknown whether these effects were sustained.[28]

Strength

A recent meta-analysis of randomized controlled trials determined that both NWB [standardized mean difference (SMD) −1.42] and WB (SMD −0.7) strengthening exercises are more efficacious for pain relief than aerobic exercise (SMD −0.45).[29] A strength of this particular analysis is that the authors only included studies with an exercise frequency of at least three sessions per week; thus, the interventions were most likely of an adequate intensity to produce a real effect. Other recent randomized controlled trials (RCTs) investigating strengthening interventions have noted significantly reduced pain following strengthening interventions but have failed to provide evidence supporting any particular intensity or dosage that may be most effective for knee OA pain.[30–32] Table 1 outlines the design, results, and relevance of recent RCTs.

A 2008 systematic review examined 18 RCTs of strengthening exercise for knee OA and noted that more than half of the studies demonstrated significant improvements in self-reported pain.[33] Among the included studies, the intervention ranged from two to seven sessions per week, each lasting from 10 to 60 minutes each, consisting of three to ten sets of three to 20 repetitions of strengthening exercise. Several of the included studies failed to publish the intensity of the intervention, and many did not report how the intervention

was progressed to produce a training effect. This again highlights the lack of useful data available for clinicians to prescribe the best, most effective strengthening program to provide pain relief for those with knee OA.

Muscle weakness, particularly in the quadriceps femoris, is associated with increased pain levels and poorer physical function.[34,35] Strong muscles are less fatigable and exhibit greater motor control, thus avoiding damaging increases in shear forces and peak joint forces that have been found during activity in those with weak muscles.[35] A rabbit study found that even a very short period of muscle weakness may be a risk factor for articular cartilage degeneration.[36] A human study found that providing pain relief via injection of local anesthetic into the knee joint resulted in improved maximum voluntary contraction of the quadriceps muscles.[37] Thus, focusing on strengthening exercises may help to avoid destructive joint forces and is likely to be associated with reduced pain levels.

Aquatic

A 2009 Cochrane review of aquatic exercise for knee and hip OA concluded that gold-level evidence supports that aquatic exercise "probably slightly reduces pain" over 3 months.[26] However, this review studied both hip and knee OA. Only one of the included studies[38] compared aquatic with land therapy specifically for those with knee OA, and a large effect was found for pain relief with aquatic resistance training (SMD 0.86) compared with land exercise. In addition, the modes of interventions provided in the studies included in the Cochrane review were widely variable. Of the included studies, treatment ranged from flexibility to strengthening to aerobics to simple joint range of motion. Dosage of exercise and length of intervention were also quite variable – interventions ranged from 6 weeks to 9 months. Thus, while this review supports the pain-relieving efficacy of aquatic exercise, it does little to determine which mode, intensity, or length of intervention may provide optimal pain relief for those with knee OA.

Other

A 2013 systematic review pooled five RCTs investigating the effects of tai chi for knee OA and found moderate evidence for pain relief in the short-term but no long-term effects.[39] However, only one of the five included studies found a large effect size for pain relief with tai chi,[40] and its participants were asked to perform tai chi daily for 48 weeks. It is unclear whether a lower frequency of tai chi would be as effective in providing pain relief.

Table 1 Summary of published studies 2008–2013 with exercise intervention for participants with knee OA and pain as an outcome variable

Authors	Intervention	N	Dosage/length of intervention	Outcome(s)	Comment(s)
Aerobic exercise					
Salacinski et al[28]	Group stationary cycling	37 (18 intervention and 17 control)	12 weeks, at least two sessions per week, 40–60 minutes per session	16.5 mm improvement in walking pain compared with control group, 95% CI 2.1–31.0	Lack of an attention control may limit findings, but group cycling may be effective in providing pain relief at 12 weeks. No follow-up beyond end of intervention period
Brosseau et al[27]	Walking intervention at moderate intensity (50%–70% of maximum heart rate)	222 (75 walking + behavioral intervention, 81 walking only, 84 self-directed control)	12 months, three sessions per week, 10-minute warm-up plus 45-minute walk per session	Significant reduction in arthritis pain among walking and behavioral intervention group at 12 and 18 months, and control at 18 months. Overall results extremely variable; effect sizes for pain relief were small	Large dropout rate in this study may limit ability to make conclusions from its results. Variability in results on pain relief makes the overall results largely inconclusive
Resistance exercise					
Farr et al[30]	Resistance training protocol: stretching, balance, flexibility, muscle strength, and aerobic components	171 (52 resistance training, 62 resistance training + self-management, 57 self-management)	Resistance training: 9 months, three sessions per week, 1 hour per session. Self-management (self-efficacy, coping, fear avoidance): 9 months, one 90-minute session per week for the first 12 weeks followed by one telephone call to reinforce knowledge for 24 weeks	Significant reduction in OA pain at 3 months for resistance group; no other significant pain reductions in other groups or at other time points. When two resistance groups were combined, significant reduction in OA pain at 3- and 9-month follow-up	Study may have been underpowered to detect an effect. Authors ultimately combined the resistance and resistance + self-management groups for analysis, which leads to suspicious conclusions. Lack of follow-up beyond the end of the intervention period also raises question of whether any pain-relieving effects were maintained
Fitzgerald et al[66]	Agility and perturbation training	183 (92 in standard exercise group and 91 in agility and perturbation training group)	Both groups received standard lower extremity stretching and strengthening and treadmill, plus home program. Agility and perturbation group also performed dynamic gait/balance and perturbation techniques using uneven surfaces	No reduction in knee pain in either group at 2-, 6-, or 12-month follow-up	Neither intervention resulted in pain reduction. Only approximately half of participants had >80% adherence with the intervention, which may have limited results
Sayers et al[31]	High- vs slow-speed strengthening	33 (12 high-speed power training, ten slow-speed strength training, eleven control)	12 weeks, three sessions per week, using knee extension strengthening equipment. High-speed group performed fast repetitions at 40% of maximum, and slow-speed group performed slow repetitions at 80% of maximum	Significant reduction in WOMAC pain subscale (P=0.02) across all groups	No differences between high-speed power training, slow-speed strength training, or control (stretching and warm-up exercises) for self-reported pain. Sample had very mild knee OA, which may not be representative of general knee OA population. Small sample size may have limited ability to detect a difference between groups
Lin[32]	Proprioceptive training vs strength training	108 (split into proprioception training, strength training, or no exercise)	8 weeks, three sessions per week, no follow-up period. Strength group performed NWB LE strengthening; proprioception group performed NWB proprioception exercises using target pedals, guided by a computer	Both interventions resulted in significant decrease in pain relative to control group; effect sizes were large for both groups. No between-group differences for pain	Both interventions may be useful for pain reduction. The proprioception exercises being entirely NWB is not consistent with real-life situations, thus their clinical utility may be limited

Balance/flexibility exercise

Study	Intervention	N	Protocol	Results	Conclusions
Ebnezar et al[67]	Hatha yoga	235 (118 yoga group, 117 control)	40 minutes of daily yoga with instructor for 2 weeks, followed by 12 weeks of daily independent practice. Control group: general therapeutic exercise	Compared with baseline, 37% reduction in walking pain at 15 days, 65% reduction in walking pain at 90 days. (Control group: 25% and 42% reductions in walking pain, respectively)	Hatha yoga resulted in greater improvements in walking pain than general therapeutic exercise but both effect sizes were very large. Minimal supervision for the intervention raises question of adherence
Wang et al[40]	Tai chi	40 (20 tai chi group, 20 attention control group)	12 weeks, two sessions per week, 60 minutes per session with instruction of tai chi master. Participants also given a DVD and handouts and encouraged to continue practicing until 48-week follow-up visit	Pain was significantly more improved in tai chi group than attention control group at 12 weeks, but these between-group differences were not maintained at 24- and 48-week follow-up	Effect sizes for tai chi group were large for both WOMAC pain subscale and VAS at all follow-up points. Tai chi is probably effective at reducing knee OA pain

Combination exercise

Study	Intervention	N	Protocol	Results	Conclusions
Hurley et al[68]	Individualized exercise program + coping-strategies intervention	418 (278 in intervention arm, 140 in usual care) (ESCAPE knee pain trial)	6 weeks, two sessions per week. 15–20 minutes of discussion of coping strategies followed by 35–40 minutes of individualized exercise prescribed by a PT	Intervention group had significantly less pain ($P<0.001$) at 6-week follow-up, but results were not maintained at 6-, 18-, or 30-month follow-ups	ESCAPE intervention effective for short-term pain relief but results not maintained. Large dropout rate at 30-month follow-up. Analysis combined data from those who performed exercise individually with PT with those in groups of eight; no information was given on whether results differed according to individual vs group mode
Abbott et al[69]	Individualized exercise program	206 (51 exercise therapy, 54 manual therapy, 50 combined exercise + manual therapy, 51 control)	Seven visits within the first 9 weeks of the trial, and two "booster" sessions in week 16; each session lasted 50 minutes. Exercise therapy consisted of warm-up/aerobic, muscle strength, stretching, and neuromuscular control exercises	Exercise, manual therapy, and manual therapy + exercise groups demonstrated significantly less pain at 1-year follow-up	Effect sizes for exercise groups were small to moderate. Intensity was fairly limited (<1 exercise session per week), which may have resulted in limited effects on pain
Jan et al[70]	High- vs low-resistance strength training	102 (34 high resistance, 34 low resistance, 34 control)	8 weeks, three sessions per week. Sessions lasted 30 minutes for the high-resistance (60% of 1RM) group and 50 minutes for the low-resistance (10% of 1RM) group	Both groups demonstrated significant improvement in pain using WOMAC pain subscale; no change in control group; large effect sizes seen for both but higher for high-resistance group	Intensity used for low-resistance group does not match what would be used clinically (10% of 1RM is likely insufficient for a training effect). Nonetheless, effect sizes for reduction in WOMAC pain are large for both the high- and low-resistance groups. No follow-up beyond intervention period raises questions regarding whether effects were maintained

Abbreviations: CI, confidence interval; ESCAPE, Enabling Self-management and Coping with Arthritic Knee Pain through Exercise; LE, lower extremity; NVB, non-weight bearing; OA, osteoarthritis; PT, physical therapist; RM, repetition maximum; VAS, visual analog scale; vs, versus; WOMAC, Western Ontario and McMaster Universities Arthritis Index; N, sample size; 1RM, one repetition maximum.

Concluding comments regarding the current evidence

The majority of published systematic reviews and meta-analyses regarding exercise for relief of OA pain include studies published in 2007 and earlier; however, several randomized clinical trials have been published since that time [see Table 1 for a summary of recent evidence (within the past 5 years)] investigating exercise interventions for pain relief in knee OA.

Perhaps the greatest limitation of the current evidence regarding the pain-relieving qualities of exercise for knee OA is the fact that interventions are not designed to specifically target pain. While some interventions such as NWB strengthening and aquatherapy aim to minimize joint forces and thus reduce pain, none of the intervention studies specifically targets the mechanisms believed responsible for generation of pain in knee OA.

Understanding the mechanisms by which knee OA pain may occur is important in furthering our ability to provide proper modes and dosages of exercise to effectively design pain-relieving exercise interventions. It has been suggested that, since knee pain reduces strength in the surrounding muscles by 5%–15%,[41] those with knee pain are trapped in a "vicious cycle" of pain, which is followed by decreased activity levels as a strategy to avoid pain, which results in increased muscle weakness. The evidence suggests that exercise can interrupt this cycle by reducing pain levels for those with OA. However, research into the specific mechanisms by which exercise provides pain relief is a developing topic.

Exercise and its potential to influence pain mechanisms in OA

Although OA is a disease characterized by degeneration of articular cartilage, cartilage is aneural, thus cannot be the source of OA pain. Much research into the genesis of knee OA pain has focused on investigation of other structures that may be producing pain, including the synovium, periosteum, subchondral bone, infrapatellar fat pad, and joint capsule.[42,43] More recently, research has begun to focus on the different mechanisms by which knee pain may occur. These mechanisms may generally be categorized into peripheral and central pathways.

Peripheral pathways

Peripheral sensitization occurs when peripheral nociceptive afferents become more spontaneously active and overly sensitive to unpleasant stimuli such as excessive movement or loading. Peripheral sensitization in OA is associated with local pain at the involved joint. The term "primary hyperalgesia" refers to increased sensitivity of peripheral nociceptors at the site of tissue damage.[44]

Local inflammatory pathways and effects of mechanical loading

While OA was previously thought a noninflammatory disease, evidence now clearly demonstrates the activation of inflammatory pathways in osteoarthritic joints, which play a role in peripheral sensitization. Cytokines are an important part of most inflammatory processes in the body. In the synovial fluid and serum of those with OA, increased levels of several cytokines, including interleukin (IL)-6, IL-8, IL-1B, and IL-15, have been observed.[45–47] Several studies have demonstrated that the elevation of cytokines in a joint with OA is related to cartilage breakdown.[43] In addition, cytokines such as IL-1B can inhibit aggrecan and collagen production, thus decreasing the joint's ability to produce extracellular matrix.[48] Cytokines have also been shown to cause upregulation of cyclooxygenase-2 (COX-2), which causes increased prostaglandins and other lipid mediators in joints with OA. Prostaglandins have been shown to play a role in inflammation and formation of new blood vessels as well as inducing cartilage damage mediated by cytokines.[49,50]

In addition to cytokines, another group of mediators called "adipokines" may play a role in inducing inflammation in osteoarthritic joints. Adipokines, derived mostly from adipose tissue, have been shown to cause cartilage breakdown and may play a role in the relationship between obesity and OA.[43,51]

Several recent studies have provided insight into how the inflammatory component of OA may be associated with peripheral sensitization. One study demonstrated that injection of an immunopotentiating agent into the knee joints of geriatric mice resulted in joint edema, macrophage infiltration, formation of new blood vessels, and sprouting of both sensory and sympathetic nerve fibers into the synovium and periosteum.[52] Studies in humans have found that inducing experimental knee pain by injecting hypertonic saline into the infrapatellar fat pad results in peripheral sensitization, measured as immediate pressure hyperalgesia on the fat pad.[53–55] Another study noted that those with increased local pain sensitivity also had higher C-reactive protein and IL-6 blood levels.[56]

Excessive joint compression and shear forces are associated with knee OA, and much research has investigated the effects that these forces may have on pain generation. While many previously thought that exercise would be detrimental

to an osteoarthritic joint, research now shows that graded exercise may promote cartilage homeostasis and reduce inflammation.

Bevill and colleagues determined that different regions of the tibial plateau respond differently to in vitro mechanical loading.[57] They hypothesized that spatial variation in gene expression of tibial plateau chondrocytes was probably due to differences in loading. In a porcine model, they confirmed that gene expression changed following mechanical loading. These results may be important in humans at risk for knee OA, specifically those with any condition that may put chondrocytes at risk of bearing unexpected loads. Specifically, knee instability due to prior anterior cruciate ligament or meniscal injury may cause mechanical loads on areas of the tibial plateau in which the chondrocytes do not typically anticipate loading – thus, the articular cartilage in that area may lack the necessary thickness and strength to handle such loads. This may lead to cartilage degeneration.

Implications for exercise and pain relief

In an osteoarthritic joint, IL-1B induces the release of prostaglandins and nitrous oxide, which ultimately results in reduced proteoglycan synthesis and reduced extracellular cartilage matrix. Chowdhury and colleagues showed that dynamic compression of chondrocytes actually counteracts this release of prostaglandins and nitrous oxide.[48] Thus, it is suggested that dynamic mechanical compression of the osteoarthritic knee joint may inhibit the inflammatory process. This compression could be mimicked during therapeutic exercise by performance of exercises that apply a dynamic, physiologic load to the knee joint. This could be achieved for those with knee OA with dynamic WB exercises.

Another study found that the cyclic tensile strain of chondrocytes in vitro results in IL-1B suppression and ultimately reduces catabolism of articular cartilage.[58] In addition, cyclic tensile strain results in increased proteoglycan and aggrecan synthesis, needed to promote cartilage homeostasis. The strain applied to chondrocytes in this study was designed to mimic continuous passive motion, a technique often used in knee rehabilitation to reduce joint stiffness and inflammation. The results of this study may support the use of continuous passive motion as an effective means of inhibiting the inflammatory process in an osteoarthritic knee joint. In addition, this may provide insight into the pathways by which repetitive exercises such as stationary cycling may provide pain relief, as was the case in the study by Salacinski and colleagues.[28]

Evidence from outside the OA literature also supports the ability of exercise to reduce peripheral sensitization. A study investigating neck pain found an immediate local hypoalgesia following completion of deep cervical flexor activation and endurance exercises, with an increase in the local pressure pain threshold.[59] The mechanism is unclear, but no systemic hypoalgesia or sympathetic nervous system excitation was observed. Because those with cervical pathology often have altered posture in the upper cervical spine, it is possible that activation of the deep upper cervical muscles relieved pain by temporarily improving posture and reducing stress on local irritated tissues. This may be applicable to the knee OA population, because it suggests that even exercises to activate specific muscles, without moving through a large arc of motion, can relieve pain, which may be particularly useful for those with end-stage knee OA who cannot tolerate exercises throughout the joint range of motion.

Overall, research suggests that peripheral mechanisms play a large role in the generation of knee OA pain and that exercise can inhibit these mechanisms to reduce pain. This information should be used for additional human studies aimed at designing specific exercise protocols to inhibit peripheral pain pathways.

Central sensitization

In addition to knee pain, those with OA often report referred pain and allodynia at a location distant from the involved joint. These phenomena are likely due to central sensitization, in which there is increased excitability and/or decreased inhibition at the spinal or cortical level. The term "secondary hyperalgesia" refers to increased sensitivity of neurons in the dorsal horn of the spinal cord in the segments corresponding to the primary site. OA pain has also been shown to activate the prefrontal limbic region of the cortex, suggesting that this region, also associated with emotional responses, may play a role in generation of OA pain.[44]

It is proposed that the phenomenon of central sensitization plays a very important role in the chronicity of OA pain, as well as pain in other chronic diseases. A few studies have also related central sensitization to OA pain. The aforementioned study by Joergensen noted that experimental knee pain caused increased temporal summation of pain signals in the surrounding musculature, which was thought to be a marker of central sensitization.[55]

It has been suggested that physical activity in general results in a decrease in excitability of the motor cortex and reduces pain by creating a motor-evoked potential drop,[27] which would seem to suggest that pain relief is possible regardless of the mode of exercise undertaken. A trial conducted in rats showed that treadmill exercise reversed signs

of neuropathic pain and resulted in increased opioid content in the regions of the brainstem that help to modulate pain.[60] The results of this study support exercise as a means to reduce central sensitization.

Two other human studies found that exercise resulted in immediate reduction in pain at sites distant from the involved area.[61,62] In the first study, people with chronic low back pain performed 25 minutes of aerobic cycle ergometry.[61] At 2 and 32 minutes post-exercise, pressure pain threshold was significantly greater at the nondominant index finger, suggesting a reduction in central sensitization. In the second study, healthy women performed submaximal isometric hand exercises.[62] Following exercise, pressure thresholds significantly increased and pain ratings significantly decreased in both the ipsilateral and contralateral hands. Although the modes of exercise used were different in the two studies, both were successful at inhibiting central pain pathways.

Another trial suggests that pain relief may occur both peripherally and centrally by reducing inflammation.[63] In that study, inflammation was triggered in mice via injection of lipopolysaccharide. Some mice were then subjected to exercise. Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), an immune response regulator, was then measured at several time points. Mice who exercised following the injection showed near-full suppression of NF-κB activation (compared with little change in NF-κB activity in mice that received the injection but did not exercise and mice that exercised but did not receive the injection). In the study, exercise inhibited inflammation systemically via NF-κB suppression both in lymph nodes distant from the injection site and locally at the injection site. In addition, both exercise prior to and exercise following the injection resulted in suppression of pro-inflammatory cytokines. The suppressive effects of exercise lasted only 24 hours following exercise. If these results were translated to a human model, it could be supposed that exercise must be performed quite frequently to maximize its inflammatory suppressive effects.

An ongoing clinical trial in Denmark (ClinicalTrials.gov identifier NCT01545258) seeks to apply a similar model in humans by investigating both peripheral and central mechanisms of exercise in knee OA. Participants are performing supervised exercise training three times per week for 1 hour and are then assessed for changes in pain threshold and temporal summation of pain. In addition, pro-inflammatory cytokines and biomarkers of cartilage breakdown in blood and urine will be measured, as well as knee inflammation on advanced imaging.

Overall, human studies investigating the mechanism of pain relief provided by exercise for people with knee OA are in their infancy. Human studies in non-OA populations indicate that both peripheral and central mechanisms play a role in pain reduction following exercise, and continued research into the specific mechanisms in those with OA is needed.

Future directions

While animal and in vitro studies are beginning to increase knowledge of how exercise may promote pain relief in an osteoarthritic joint, these theories have not yet been adequately tested in humans. Many studies continue to investigate the pain-relieving effects of exercise, but without knowledge of the particular mechanisms by which pain relief may occur, it is difficult to determine the most beneficial mode and dosage of exercise. Thus, more research needs to be done in humans to understand the mechanisms by which exercise reduces pain and to determine appropriate exercise parameters to maximize pain relief.

A particular challenge in the study of peripheral and central mechanisms by which OA causes pain and by which exercise relieves such pain is the limitation of methods to identify pain. Most instruments for identifying pain-processing mechanisms are laboratory based, thus expensive and not terribly clinically relevant.[64] Pressure algometers have been shown to be fairly reliable and inexpensive tools for measuring general sensitivity to pressure stimuli but are not yet widely used in clinics and do not distinguish between peripheral and central pain mechanisms.[64] The ability to clinically determine whether a person's pain is related more to peripheral or central mechanisms may significantly assist in treatment decisions, thus this is an area ripe for research. It is quite possible that certain exercise approaches will be useful for peripheral pain, while others may be more useful for central pain. Research needs to be done to identify those who will respond to certain types of pain-relieving exercises depending on the type of pain experienced.

In addition to selection of an appropriate mode and dosage of exercise to provide pain relief, further research is needed to explore other factors that may affect the outcome of exercise on pain. For example, is there a positive interaction between exercise and pharmacologic treatment? Does timing of exercise and medication schedule affect pain relief? Disease severity has been shown to be a potential predictor of responsiveness to rehabilitation;[65] thus, different exercise approaches may need to be used for those with early versus late-stage knee OA in order to provide optimal pain relief.

Behavioral factors are also likely to influence the outcomes of exercise. Lower fear of physical activity has been associated with increased odds of a positive response to exercise.[66] Pain in OA is also related to a number of psychological variables such as anxiety, depression, poor pain-coping skills, and greater fear avoidance.[34] The specific effects of these variables on the outcomes of exercise for those with knee OA need to be examined.

Conclusion

Overall, research consistently supports exercise as an effective means of relieving pain. As the specific mechanisms of OA pain and how exercise may interrupt these pain pathways are discovered, this information can be used by clinical researchers to determine optimal mode and dosage of exercise to provide maximal pain relief to those with knee OA.

Disclosure

The authors declare no conflicts of interest in this work.

References

1. 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(2):137–162.
2. Centers for Disease Control and Prevention (CDC). Osteoarthritis [web page on the Internet]. Atlanta, GA: CDC; nd [updated September 1, 2011]. Available from: http://www.cdc.gov/arthritis/basics/osteoarthritis.htm. Accessed May 13, 2013.
3. Slemenda CW. The epidemiology of osteoarthritis of the knee. *Curr Opin Rheumatol*. 1992;4(4):546–551.
4. Ettinger WH, Davis MA, Neuhaus JM, Mallon KP. Long-term physical functioning in persons with knee osteoarthritis from NHANES. I: Effects of comorbid medical conditions. *J Clin Epidemiol*. 1994;47(7):809–815.
5. Fitzcharles MA, Lussier D, Shir Y. Management of chronic arthritis pain in the elderly. *Drugs Aging*. 2010;27(6):471–490.
6. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. *Lancet*. 2005;365(9463):965–973.
7. Lohmander S, Johnell O, Pederson NL. Genetic contribution to severe osteoarthritis of the hip and knee leading to arthroplasty: a twin study [abstract]. *Arthritis Rheum*. 2004;50:S140.
8. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham study. *Ann Intern Med*. 1988;109(1):18–24.
9. Widmyer MR, Utturkar GM, Leddy HA, et al. High body mass index is associated with increased diurnal strains in the articular cartilage of the knee. *Arthritis Rheum*. Epub July 1, 2013.
10. Hawker GA. The challenge of pain for patients with OA. *HSS J*. 2012;8(1):42–44.
11. Katz P, Lee F. Racial/ethnic differences in the use of complementary and alternative medicine in patients with arthritis. *J Clin Rheumatol*. 2007;13(1):3–11.
12. Bjordal JM, Johnson MI, Lopes-Martins RA, Bogen B, Chow R, Ljunggren AE. Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and meta-analysis of randomised placebo-controlled trials. *BMC Musculoskelet Disord*. 2007;8:51.
13. Vance CG, Rakel BA, Blodgett NP, et al. Effects of transcutaneous electrical nerve stimulation on pain, pain sensitivity, and function in people with knee osteoarthritis: a randomized controlled trial. *Phys Ther*. 2012;92(7):898–910.
14. Peterson SG, Beyer N, Hansen M, et al. Nonsteroidal anti-inflammatory drug or glucosamine reduced pain and improved muscle strength with resistance training in a randomized controlled trial of knee osteoarthritis patients. *Arch Phys Med Rehabil*. 2011;92(8):1185–1193.
15. Jamtvedt G, Dahm KT, Christie A, et al. Physical therapy interventions for patients with osteoarthritis of the knee: an overview of systematic reviews. *Phys Ther*. 2008;88(1):123–136.
16. Somers TJ, Blumenthal JA, Guilak F, et al. Pain coping skills training and lifestyle behavioral weight management in patients with knee osteoarthritis: a randomized controlled study. *Pain*. 2012;153(6):1199–1209.
17. Marcum ZA, Perera S, Donohue JM, et al; Health, Aging and Body Composition Study. Analgesic use for knee and hip osteoarthritis in community-dwelling elders. *Pain Med*. 2011;12(11):1628–1636.
18. American Academy of Orthopaedic Surgeons (AAOS). *Treatment of Osteoarthritis of the Knee: Evidence-Based Guideline*. 2nd ed. Rosemont, IL: AAOS; 2013. Available from: http://www.aaos.org/research/guidelines/guidelineoaknee.asp. Accessed July 1, 2013.
19. Hochberg MC, Altman RD, April KT, et al; American College of Rheumatology. 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(4):465–474.
20. Hootman JM, Macera CA, Ham SA, Helmick CG, Sniezek JE. Physical activity levels among the general US adult population and in adults with and without arthritis. *Arthritis Rheum*. 2003;49(1):129–135.
21. 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(1):67–73.
22. Jansen MF, Viechtbauer W, Lenssen AF, Hendriks EJM, 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.
23. Iwamoto J, Sato Y, Takeda T, Matsumoto H. Effectiveness of exercise for osteoarthritis of the knee: A review of the literature. *World J Orthop*. 2011;2(5):37–42.
24. Fransen M, McConnell S. Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev*. 2008;(4):CD004376.
25. Bosomworth NJ. Exercise and knee osteoarthritis: benefit or hazard? *Can Fam Physician*. 2009;55(9):871–878.
26. Bartels EM, Lund H, Hagen KB, Dagfinrud H, Christensen R, Danneskiold-Samsøe B. Aquatic exercise for the treatment of knee and hip osteoarthritis. *Cochrane Database Sys Rev*. 2007;(4):CD005523.
27. Brosseau L, Wells GA, Kenny GP. The implementation of a community-based aerobic walking program for mild to moderate knee osteoarthritis: a knowledge translation randomized controlled trial: part II: clinical outcomes. *BMC Public Health*. 2012;12:1073.
28. Salacinski AJ, Krohn K, Lewis SF, Holland ML, Ireland K, Marchetti G. The effects of group cycling on gait and pain-related disability in individuals with mild-to-moderate knee osteoarthritis: a randomized controlled trial. *J Orthop Sports Phys Ther*. 2012;42(12):985–995.
29. Tanaka R, Ozawa J, Kito N, Moriyama H. Efficacy of strengthening or aerobic exercise on pain relief in people with knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Clin Rehabil*. Epub July 4, 2013.
30. Farr JN, Going SB, McKnight PE, Kasie S, Cussler EC, Cornett M. Progressive resistance training improves overall physical activity levels in patients with early osteoarthritis of the knee: a randomized controlled trial. *Phys Ther*. 2010;90(3):356–366.

31. Sayers SS, Gibson K, Cook CR. Effect of high-speed power training on muscle performance, function, and pain in older adults with knee osteoarthritis: a pilot investigation. *Arthritis Care Res (Hoboken)*. 2012;64(1):46–53.

32. Lin D, Lin CJ, Lin Y, Jan M. Efficacy of 2 non-weight-bearing interventions, proprioception training versus strength training, for patients with knee osteoarthritis: a randomized clinical trial. *J Orthop Sports Phys Ther*. 2009;39(6):450–457.

33. Lange AK, Vanwanseele B, Fiatarone Singh MA. Strength training for treatment of osteoarthritis of the knee: a systematic review. *Arthritis Rheum*. 2008;59(10):1488–1494.

34. Bennell KL, Ahamed Y, Bryant C, et al. A physiotherapist-delivered integrated exercise and pain coping skills training intervention for individuals with knee osteoarthritis: a randomised controlled trial protocol. *BMC Musculoskelet Disord*. 2012;13:129.

35. Valderrabano V, Steiger C. Treatment and Prevention of Osteoarthritis through Exercise and Sports. *J Aging Res*. 2011;2011:Article ID 374653.

36. Herzog W, Longino D. The role of muscles in joint degeneration and osteoarthritis. *J Biomech*. 2007;40 Suppl 1:S54–S63.

37. Hassan BS, Doherty SA, Mockett S, Doherty M. Effect of pain reduction on postural sway, proprioception, and quadriceps strength in subjects with knee osteoarthritis. *Ann Rheum Dis*. 2002;61(5):422–428.

38. Wyatt FB, Milam S, Manske RC, Deere R. The effects of aquatic and traditional exercise programs on persons with knee osteoarthritis. *J Strength Cond Res*. 2001;15(3):337–340.

39. Lauche R, Langhorst J, Dobos G, Cramer H. A systematic review and meta-analysis of Tai Chi for osteoarthritis of the knee. *Complement Ther Med*. 2013;21(4):396–406.

40. Wang C, Schmid CH, Hibberd PL, et al. Tai Chi is effective in treating knee osteoarthritis: a randomized controlled trial. *Arthritis Rheum*. 2009;61(11):1545–1553.

41. Henriksen M, Rosager S, Aaboe J, Graven-Nielsen T, Bliddal H. Experimental knee pain reduces muscle strength. *J Pain*. 2011;12(4):460–467.

42. Kidd BL. Osteoarthritis and joint pain. *Pain*. 2006;123(1–2):6–9.

43. Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. *Ther Adv Musculoskel Dis*. 2013;5(2):77–94.

44. Lluch Girbés E, Nijs J, Torres-Cueco R, López Cubas C. Pain treatment for patients with osteoarthritis and central sensitization. *Phys Ther*. 2013;93(6):842–851.

45. Kaneko S, Satoh T, Chiba J, Ju C, Inoue K, Kagawa J. Interleukin-6 and interleukin-8 levels in serum and synovial fluid of patients with osteoarthritis. *Cytokines Cell Mol Ther*. 2000;6(2):71–79.

46. Scanzello C, Umoh E, Pessler F, et al. Local cytokine profiles in knee osteoarthritis: elevated synovial fluid interleukin-15 differentiates early from end-stage disease. *Osteoarthritis Cartilage*. 2009;17(8):1040–1048.

47. Sohn D, Sokolove J, Sharpe O, et al. Plasma proteins present in osteoarthritic synovial fluid can stimulate cytokine production via Toll-like receptor 4. *Arthritis Res Ther*. 2012;14(1):R7.

48. Chowdhury TT, Bader DL, Lee DA. Dynamic compression counteracts IL-1beta induced iNOS and COX-2 activity by human chondrocytes cultured in agarose constructs. *Biorheology*. 2006;43(3–4):413–429.

49. Martel-Pelletier J, Pelletier JP, Fahmi H. Cyclooxygenase-2 and prostaglandins in articular tissues. *Semin Arthritis Rheum*. 2003;33(3):155–167.

50. Moreno-Rubio J, Herrero-Beaumont G, Tardio L, Alvarez-Soria MA, Largo R. Nonsteroidal antiinflammatory drugs and prostaglandin E(2) modulate the synthesis of osteoprotegerin and RANKL in the cartilage of patients with severe knee osteoarthritis. *Arthritis Rheum*. 2010;62(2):478–488.

51. Conde J, Scotece M, Gómez R, Lopez V, Gómez-Reino JJ, Gualillo O. Adipokines and osteoarthritis: novel molecules involved in the pathogenesis and progression of disease. *Arthritis*. 2011;2011: Article ID 203901.

52. Jimenez-Andrade JM, Mantyh PW. Sensory and sympathetic nerve fibers undergo sprouting and neuroma formation in the painful arthritic joint of geriatric mice. *Arthritis Res Ther*. 2012;14(1):R101.

53. Henriksen M, Simonsen EB, Alkjaer T, et al. Increased joint loads during walking – a consequence of pain relief in knee osteoarthritis. *Knee*. 2006;13(6):445–450.

54. Sørensen TJ, Langberg H, Hodges PW, Bliddal H, Henriksen M. Experimental knee joint pain during strength training and muscle strength gain in healthy subjects: a randomized controlled trial. *Arthritis Care Res*. 2012;64(1):108–116.

55. Joergensen TS, Henriksen M, Danneskiold-Samsoee B, Bliddal H, Graven-Nielsen T. Experimental knee pain evoke spreading hyperalgesia and facilitated temporal summation of pain. *Pain Med*. 2013;14(6):874–883.

56. Lee YC, Lu B, Bathon JM, et al. Pain sensitivity and pain reactivity in osteoarthritis. *Arthritis Care Res (Hoboken)*. 2011;63(3):320–327.

57. Bevill SL, Briant PL, Levenston ME, Andriacchi TP. Central and peripheral region tibial plateau chondrocytes respond differently to in vitro dynamic compression. *Osteoarthritis Cartilage*. 2009;17(8):980–987.

58. Xu Z, Buckley MJ, Evans CH, Agarwal S. Cyclic tensile strain acts as an antagonist of IL-1 beta actions in chondrocytes. *J Immunol*. 2000;165(1):453–460.

59. O'Leary S, Falla D, Hodges PW, Jull G, Vincenzino B. Specific therapeutic exercise of the neck induces immediate local hypoalgesia. *J Pain*. 2007;8(11):832–839.

60. Stagg NJ, Mata HP, Ibrahim MM, et al. Regular exercise reverses sensory hypersensitivity in a rat neuropathic pain model: role of endogenous opioids. *Anesthesiology*. 2011;14(4):940–948.

61. Hoffman MD, Shepanski MA, MacKenzie SP, Clifford PS. Experimentally induced pain perception is acutely reduced by aerobic exercise in people with chronic low back pain. *J Rehabil Res Dev*. 2005;42(2):183–190.

62. Kotlyn KF, Umeda M. Contralateral attenuation of pain after short-duration submaximal isometric exercise. *J Pain*. 2007;8(11):887–892.

63. Knapik D, Young N, Blazek A, et al. Exercise antagonizes local and systemic inflammation via suppression of NF-kB activation [abstract]. *Osteoarthritis Cartilage*. 2013;21:S561–S562.

64. Sterling M. Pressure algometry: what does it really tell us? *J Orthop Sports Phys Ther*. 2011;41(9):623–624.

65. Fransen M, Crosbie J, Edmonds J. Physical therapy is effective for patients with osteoarthritis of the knee: a randomized controlled clinical trial. *J Rheumatol*. 2001;28(1):156–164.

66. Fitzgerald GK, Piva SR, Gil AB, Wisniewski SR, Oddis CV, Irrgang JJ. Agility and perturbation training techniques in exercise therapy for reducing pain and improving function in people with knee osteoarthritis: a randomized clinical trial. *Phys Ther*. 2011;91(4):452–469.

67. Ebnezar J, Nagarathna R, Yogitha B, Nagendra HR. Effects of an integrated approach of hatha yoga therapy on functional disability, pain, and flexibility in osteoarthritis of the knee joint: a randomized controlled study. *J Alter Complement Med*. 2012;18(5):463–472.

68. 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 (Hoboken)*. 2012;64(2):238–247.

69. Abbott JH, Robertson MC, Chapple C, et al; MOA Trial Team. 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(4):525–534.

70. Jan M, Lin J, Liau J, Lin Y, Lin D. Investigation of clinical effects of high- and low-resistance training for patients with knee osteoarthritis: a randomized controlled trial. *Phys Ther*. 2008;99(4):427–436.