[Primary Care]

Nonoperative Treatment Approach to Knee Osteoarthritis in the Master Athlete

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Context: Middle-age and elderly participants in athletic activities frequently encounter the chronic disabling process of osteoarthritis. Knowledge of the treatment of knee osteoarthritis is needed to keep the master athlete active.

Objective: This article reviews the current scientific evidence regarding recommendations for the maturing athlete, specifically discussing the strengths and weaknesses of dietary and lifestyle modifications, physical therapy, bracing, supplements, pharmacotherapies, and biologics in the management of knee osteoarthritis.

Level of Evidence: Level 4.

Conclusion: These treatment modalities can help keep the aging athlete active, which in itself plays an important role in reducing the symptoms of knee osteoarthritis.

Keywords: knee; osteoarthritis; elderly; athlete; nonoperative treatments

Participation in physical activity and sports among US adults has increased in recent years. In 2010, 20.7% of adults met both aerobic activity and muscle-strengthening guidelines compared with only 14.5% in 1998.[11] The benefits of exercise in this expanding group of aging athletes are numerous, including improved aerobic exercise capacity, cardiovascular function, and maintenance of lean body mass.[14,21,33] Participation in sports and exercise also improves and extends life by reducing an individual's risk of many diseases, such as thromboembolic stroke, hypertension, type 2 diabetes, osteoporosis, obesity, and cognitive decline.[19,20,28,31,39,40,69] Keeping master athletes active should therefore be a priority.

Knee osteoarthritis (OA), a frequent complication of sports-related joint injury, is the most prevalent musculoskeletal disease in the master athlete.[48] Characterized by cartilage loss and inflammation of the synovium, patients are often plagued by pain and discomfort.[22] Physical examination findings include warmth, swelling, weakness, and restricted range of motion. Radiographs reveal osteophytes, subchondral sclerosis and cysts, joint space narrowing, and effusions (Figure 1).[80]

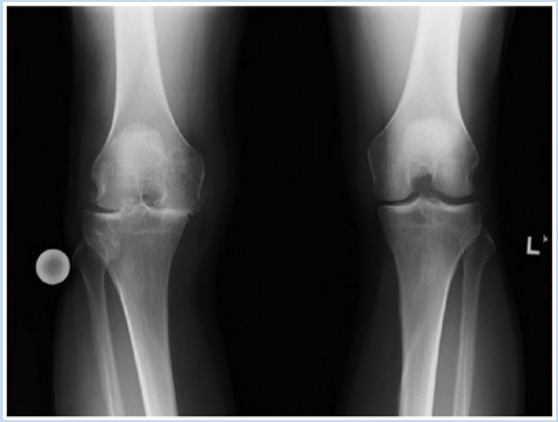

Figure 1. Rosenberg view radiograph of knees. Note the right knee with severe osteoarthritis characterized by osteophytes, subchondral sclerosis and cysts, joint space narrowing, and effusion.

Increasing age is the primary risk factor for knee OA. Mechanical factors such as excess body mass, joint injury, occupation (excessive mechanical stress), and structural malalignment (varus/valgus) can also accelerate the process. In addition to mechanical factors, the biochemical environment of the joint plays an integral role. Proinflammatory cytokines (interleukin-1β [IL-1β], IL-6, IL-8, and tumor necrosis factor α) are elevated in the serum and synovial fluid of those with OA and mediate synovial tissue inflammation and the destruction of cartilage macromolecules.[32,44] However, the causes of increased expression of these cytokines and the extent of their role in the pathophysiology of OA have not been fully elucidated. Evidence that adipose tissue may be a contributing factor to OA via complex mechanisms include OA in nonweightbearing joints, proinflammatory cytokines in adipose tissue, and infrapatellar fat pad inflammation associated with knee OA.[42]

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Just as there is an array of interacting risk factors for the development of knee OA, there are various preventative and treatment measures that can be utilized, often in combination. The goal of this article is to present an evidence-based approach to the nonsurgical treatment of knee OA. Treatment modalities that will be discussed include weight loss and exercise recommendations, physical therapy, bracing, taping, orthotics, supplements, pharmacotherapies, and biologics.

WEIGHT LOSS AND EXERCISE

Lifestyle factors such as body mass index and physical activity play an instrumental role in the pathogenesis of OA of the knee. For patients to become motivated to make what are often tough changes, it is helpful to understand how behavioral choices contribute to the development of OA, and the beneficial effect of changing weight, activity levels, and types of exercise.

Obesity is one of the most prevalent, influential, and modifiable risk factors of knee OA.[25,57] In fact, obesity has been found to be the primary preventable cause of OA in women and the second most preventable cause of OA in men after major knee injury.[25] Obese individuals have a 4- to 10-fold higher risk of developing OA of the knee compared with lower or normal weight counterparts; obesity alone accounts for one third of all knee OA cases.[25,57] The mechanism is in large part due to excess loads across the knee joint, which experiences loading equal to approximately 4 times the body weight during the single-leg stance of walking.[25,54] Additionally, obesity induces OA in nonweightbearing joints through a systemic inflammatory effect.[34] The Framingham study reported that weight loss of 2 body mass index units (approximately 5.1 kg) over 10 years decreased the risk of knee OA by 50% in overweight women. A meta-analysis demonstrated that losing 5% of baseline body weight reduces disability in those who already have symptomatic knee OA.[17,26]

Some studies have questioned whether weight loss through dieting without exercise reduces the symptoms of OA. A randomized controlled trial of 159 obese patients with knee OA reported that a low-energy diet-induced weight loss intervention lasting 16 weeks resulted in a mean weight loss of 12.9 kg, 1.9 kg of which was lean body mass. Although the diet group's absolute muscle strength decreased by 3% to 4%, their body mass–normalized muscle strength increased by 11% to 12% and the participants had improved self-reported disability and pain.[36] This study provides evidence that dieting alone can relieve the symptoms of knee OA in obese patients. An exercise regimen should be initiated at the same time to help maintain weight loss.

In addition to promoting weight loss, light to moderately intense exercise plays a pivotal role in combating knee OA by increasing knee stability and by creating an anabolic environment secondary to mechanical stimulation of the joint. Regular cyclic loading of the knee stimulates the synthesis and remodeling of cartilage to create a tougher protective joint surface, whereas continuous compression can lead to cartilage necrosis and degradation.[3] Additionally, quadriceps weakness has been identified as a risk factor for the development and progression of symptomatic knee OA in longitudinal studies, especially in women.[38,70,71] The greater role of quadriceps weakness in women with OA is attributable to a mean quadriceps strength roughly half that in men (72.0 vs 125.7 Nm). This leads to decreased stability at the knee joint during loading.[70] A 5-week-long exercise regimen consisting of ten 30-minute quadriceps strengthening sessions has been shown to increase strength, improve objective function, and decrease subjective disability in those with knee OA. These results were maintained 6 months later when patients continued performing these exercises at home for 20 to 30 minutes a week (see online appendix, available at http://sph.sagepub.com/content/suppl).[41]

A common misconception is that moderate-intensity exercise may exacerbate OA pain or accelerate the degeneration; on the contrary, a comprehensive review of randomized controlled trials by the American Geriatric Society refuted this misconception, finding that pain and morbidity are reduced with increased physical activity.[1] This prompted the society to formulate an exercise prescription that can help guide patients with OA, outlining evidence-based recommendations for exercise intensity, volume, and frequency. Roddy et al compiled supplemental recommendations for exercise that differentiates the levels of evidence supporting each proposition.[67] Swimming, cycling, and elliptical exercises are excellent low-impact aerobic activity choices for individuals with symptomatic knee OA, which can limit other higher impact exercise options.[76]

Higher impact activities are more controversial. Numerous studies warn against such activities because of the misconception that high impact joint loading damages cartilage. However, long-time recreational runners who have had regular running schedules over many years have been assessed in multiple studies without elevated rates of OA.[10] For example, a study that followed 45 long-distance runners (mean age, 58 years) for almost 2 decades found no association between running and accelerated radiographic OA compared with controls. In fact, 6.7% of the runners initially demonstrated radiographic OA compared with none of the controls; yet, at final follow-up, only 20% of runners compared with 32% of controls demonstrated these same radiographic findings. Only 2.2% of runners demonstrated severe OA, compared with 9.4% of controls.[13] In an attempt to evaluate the impact of running on elderly disability and overall health, a 13-year prospective study of 370 runners club members who were at least 50 years old, compared with 249 controls, reported that running protected against disability and early mortality, with controls having a 3.3-times-higher rate of death.[88] Therefore, with evidence on the side of running in slowing the development and/or progression of knee OA, there appears little reason for physicians to discourage running in this patient population.

PHYSICAL THERAPY

Physical therapeutic treatments for knee OA aim to reduce loads across the joint and include activity modification, low-impact exercise, flexibility, and strength training. Significant reductions in pain associated with knee OA have been demonstrated with a therapist-administered exercise program.[82] Self-reported knee pain and disease-specific physical function in patients with knee OA also improve with exercise. A Cochrane review analyzed 32 clinical trials studying the effects of land-based therapeutic exercise. Exercise programs varied from basic quadriceps-strengthening and aerobic-walking programs to more advanced programs, including manual therapy, truncal and lower limb strengthening, and proprioceptive training. This meta-analysis showed that exercise programs resulted in a mean treatment benefit for both knee pain (standardized mean difference, 0.40; 95% confidence interval, 0.30 to 0.50) and physical function (standardized mean difference, 0.37; 95% confidence interval, 0.25 to 0.49) similar to the pain relief provided by nonsteroidal anti-inflammatory drugs (NSAIDs).[30]

BRACING, KNEE TAPING, AND ORTHOTICS

The most widely used brace for knee OA over the past decade is the unloader brace, which is indicated for malaligned knees associated with unicompartmental arthritis. The unloader brace improves knee alignment so that the ground reaction force is reduced in the affected compartment of the knee (either medial or lateral) and increased in the unaffected compartment. Recent studies show that unloader knee braces reduce knee pain in patients with OA, particularly in those with medial compartment knee OA.[45] In a randomized controlled trial, the unloader braces had better outcomes compared with other braces in 119 patients.[45] In a short-term study of 10 patients, custom unloader braces reduced stiffness and improved function in patients with knee OA to a greater extent than the off-the-shelf variety.[23] Komistek et al reported that 12 of 15 patients had condylar separation on fluoroscopy and subsequent pain relief with unloader bracing.[46] Moreover, unloader brace use may reduce personal dependence on analgesics such as NSAIDs and possibly slow down the progression of OA.[45] However, long-term brace use is unlikely. In a prospective study of 30 patients with unicompartmental OA of the knee treated with an unloader brace, at a mean follow-up of 2.7 years, only 41% of 30 patients were still using the brace, and 24% had undergone arthroplasty. None of the patients reported brace use at a mean follow-up of 11.2 years, and 58.6% had undergone arthroplasty at a mean 3.9 years following brace prescription.[92]

Therapeutic knee taping may improve pain scores in patients with knee OA by improving the alignment of the patellofemoral joint and unloading inflamed soft tissues (Figure 2). In a blinded randomized study, therapeutic tape was applied to provide medial glide, medial tilt, and anteroposterior tilt to the patella.[37] Tape was also applied to either the infrapatellar fat pad or pes anserine bursa to reduce soft tissue swelling. After 6 weeks, 73% of participants reported improved pain, compared with 10% of those not using tape ($P = 0.00$).[37] A systematic review and meta-analysis of the efficacy of patella taping for patellofemoral OA showed that tape exerting a medially directed force on the patella decreased chronic knee pain on a 100-mm scale by 16.1 mm ($P < 0.01$) compared with no tape and by 10.9 mm ($P < 0.01$) compared with sham taping, supporting the notion that patellar taping has a beneficial therapeutic effect.[91]

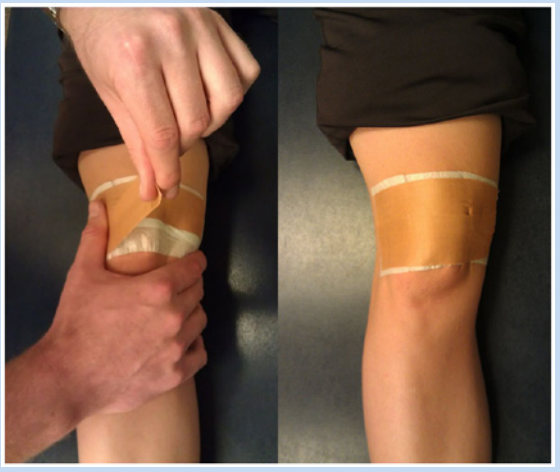

Figure 2. Therapeutic McConnell knee taping applied to improve patellofemoral alignment by supporting medial glide.

Shoe orthotic implants that aim to unload one side of the knee have also been investigated as a treatment for unicompartmental knee arthritis. A systematic review by Malvankar et al showed that there was insufficient evidence to conclude that lateral wedge orthotics were an effective treatment for medial compartment OA.[52] However, orthotics may still provide symptomatic relief, and patients with early OA and high body mass index were likely to experience the largest benefit. Benefits at 1 month were maintained at 1 year and suggest that prolonged use may be beneficial.[52]

SUPPLEMENTS AND DIETARY FACTORS

Glucosamine and chondroitin sulfate are popular over-the-counter supplements often taken in combination for OA symptoms. They have minimal side effects however, their efficacy remains controversial.[18] Glucosamine is an amino sugar precursor for the synthesis of glycosylated proteins, lipids, and glycosaminoglycans, a major component of articular cartilage. Chondroitin sulfate is a sulfated glycosaminoglycan that is also a constituent of articular cartilage. The hydrocolloid

properties of glycosaminoglycans enable cartilage to resist compression, and through partial absorption from the intestine, these supplements could supply a degenerative joint with the building blocks for restoring cartilage.[87] However, evidence is lacking and trials have not consistently demonstrated a clinical benefit. A 2009 Cochrane review of 25 studies with a total of 4963 patients with OA reported that 1500 mg of glucosamine daily had an excellent safety profile, reduced pain by 22%, and improved function by 11%, resulting in no detectable difference in efficacy compared with NSAIDs.[84] Additionally, 2 studies provided "high-quality" evidence for a small increase in minimum joint width at a mean 3 years of follow-up.[59,64] When only the best studies were included in the analysis, no benefits were demonstrated.[84] Selective meta-analyses of chondroitin or the combination of the 2 supplements have reported similar conclusions, demonstrating no overall benefit in pain reduction or maintenance of joint space for knee OA. Industry-independent studies have consistently demonstrated less beneficial effects than industry-funded trials.[65,87] Based on these findings, the American Academy of Orthopaedic Surgeons currently recommends against prescribing glucosamine and chondroitin for knee OA.[66]

Even though glucosamine and chondroitin are unlikely to provide clinically meaningful relief for most patients with knee OA, those with more advanced disease may nevetheless experience a benefit. A multicenter, double-blind, placebo- and celecoxib-controlled glucosamine/chondroitin arthritis intervention trial of over 1500 patients with knee OA showed that while the supplements had no significant overall effect on pain reduction, the subgroup of patients with moderate to severe knee pain experienced significant relief with a combination of glucosamine and chondroitin compared with a placebo.[18] However, this finding was the result of an exploratory analysis and not a primary outcome of the study, so it may be subject to a type 1 error.

Other supplements and dietary factors, such as vitamin C, avocado soybean unsaponifiable, and fatty acid intake, may help treat knee OA. The progression of OA is thought to involve damage by free radicals. The antioxidant properties of these supplements may help quell intra-articular inflammation if increased in the diet.[77] However, clinical studies have shown minimal gains. While one study reported that higher amounts of vitamin C intake lowered the incidence of knee OA by 11% with no effect on progression,[61] other studies have found no association.[35,90] Daily doses of 300 mg or more of avocado soybean unsaponifiable may decrease NSAID and analgesic intake by more than half,[2] with similar efficacy to 400 mg chondroitin sulfate 3 times daily after 6 months.[58] Omega-3 polyunsaturated fatty acid plasma levels have an inverse association with patellofemoral cartilage loss. Omega-6 polyunsaturated fatty acid plasma levels are associated with synovitis. Increased consumption of saturated fatty acids may increase bone marrow lesions in the knee.[4,89] Overall, the benefits of these supplements and dietary factors are dubious and should not be the focus of knee OA treatment.

ORAL PHARMACOTHERAPIES

Oral pharmaceuticals consist of inexpensive analgesics such as acetaminophen, NSAIDs, and opioids. These provide some degree of symptomatic relief but do little to halt or reverse the degenerative process.[79] Acetaminophen is well tolerated, and according to a Cochrane review, it was as efficacious as NSAIDs for mild knee and hip OA-related pain. NSAIDs were superior for moderate to severe levels of pain.[85] NSAIDs have potential side effects involving the gastrointestinal, renal, hepatic, and cardiac systems that pose a substantial hazard to those with advanced age.[76] Opioids also have substantial drawbacks.[76] Therefore, the generally accepted treatment symptomatic relief is acetaminophen as the first line, NSAIDs if acetaminophen is not adequate, and opioids as a last resort.[76]

TOPICAL PHARMACOTHERAPIES

The systemic side effects of oral therapy make topicals an appealing option. Topical NSAIDs are well tolerated with lower systemic levels compared with oral administration. About 20% of patients experience dry or mildly irritated skin at the application site.[72,83,86] Oral and topical diclofenac are equivalent in relieving pain and improving physical function for knee OA.[72,83,86]

INJECTABLE PHARMACOTHERAPIES

Intra-articular injection options for knee OA include corticosteroids, hyaluronic acid (viscosupplementation), and botulinum toxin. A study of 240 consecutive knee injections showed that the lateral midpatellar technique was the most accurate (93% success rate) compared with anteromedial (75%) and anterolateral (71%).[43] A Cochrane review reported that intra-articular corticosteroid injections provided significant short-term pain relief up to 4 weeks, with no effect on knee function.[6] It appears that the short-term effect of steroids can be prolonged with repetitious dosing every 3 months.[63] However, there is some concern for the negative consequences of certain injected corticosteroid classes on articular cartilage. In horses, betamethasone esters (Schering-Plough Animal Health Corp, Union, New Jersey) and triamcinolone acetonide (Bristol-Myers Squibb, Fort Dodge, Iowa) had no deleterious side effects and were chondroprotective, whereas methylprednisolone acetate (Pharmacia and Upjohn Co, Kalamazoo, Michigan) had deleterious effects.[53] A systematic review in 2012 showed 1A+ level evidence supporting short-term pain relief and functional improvement with intra-articular corticosteroids for knee OA and 2B+ level evidence supporting triamcinolone hexacetonide over triamcinolone acetonide.[15]

Hyaluronic acid is a naturally occurring substance found in the synovial fluid. Injection of a highly purified, cross-linked form allows for longer retention within the synovial fluid to supplement joint viscosity, lubrication, and absorption of compressive forces.[81] A Cochrane review of viscosupplementation found that hyaluronic acid had an

effect for up to 6 months, with peak benefit at 5 to 13 weeks after injection. Improvement in pain, function, and global assessment was comparable with oral NSAIDs, with more local reactions but fewer systemic side effects.[7] However, on the contrary, a more recent meta-analysis demonstrated moderate short-term pain relief but concluded that the risk for adverse events was not negligible. The overall benefit was small and clinically irrelevant.[68] Thus, viscosupplementation may be considered as a presurgical option for patients with elevated surgical risk who need treatment in addition to exercise and other available analgesic therapies.[15]

Intra-articular botulinum toxin is a less widely used therapy that may have antinociceptive and anti-inflammatory actions.[74] Botulinum toxin inhibits release of substance P and calcitonin gene–related protein neuropeptides that mediate neurogenic inflammation.[8,50,73] Three randomized controlled trials using injections of 25 to 200 units of type A botulinum toxin demonstrated significant short-term improvements in pain and function. Another demonstrated short-term efficacy equivalent to intra-articular steroids.[9,51,74,75] A systematic review reported 2B+ level evidence supporting type A botulinum toxin's pain-relieving effect for arthritic knees.[15]

BIOLOGICS

Growth factors, platelet-rich plasma (PRP), concentrated bone marrow aspirate, and other stem cell therapies intended to treat inflammatory or degenerative conditions have spawned much interest in recent years. Previous studies have shown that the application of concentrated growth factors and autologous stem cells may stimulate healing in tissues that have a limited ability for self-regeneration.[29,60]

PRP has been researched since the 1970s, and has recently experienced a rapid recent expansion of applications including intra-articular injection for knee OA.[29,60] The rationale for using PRP for treatment of knee OA is that intact platelet α-granules contain a large assortment of growth factors that affect articular cartilage, which are subsequently released into the surrounding environment upon platelet activation.[60] A 2-year follow-up of 90 patients after PRP injections showed the benefit duration to vary widely, with a mean of approximately 11 months (± 8 months) in patients with OA.[27] Two prospective randomized trials demonstrated superior pain reduction and functional improvement compared with viscosupplementation at 6 months and suggested greater benefit in those younger than 50 years with early OA.[47,78] In light of this evidence, PRP appears to be safe in the short term, aside from a transient increase in knee pain following injection in a small percentage of patients.[27,47,78]

However, mainstream application of PRP to treat knee OA is limited by several factors. The true efficacy, ideal platelet concentration, and safety of PRP have not been determined in long-term, high-powered randomized trials.[24,49] Biologics such as PRP have not yet been approved by the Federal Drug Administration to treat OA, so according to section 361 of the Public Health Service Act, they can only undergo "minimal manipulation."[62] The generally accepted interpretation is that manipulation beyond extracting and concentrating, such as heating to activate signaling molecules (as is done in some other countries), is not approved in the United States.[5] In addition, most medical insurance companies do not reimburse for PRP to treat knee OA.

The use of stem cell therapy to treat knee OA is still in early development, however preliminary results appear promising. Mesenchymal stem cells from bone marrow and adipose tissues are capable of differentiation into chondrocytes and can be injected into the knee joint along with platelets and growth factors after concentrating or culturing.[16] In animal studies, mesenchymal stem cells incorporated into damaged articular cartilage improved the clinical, radiographic, and histopathologic features of joints compared to controls.[55,56] Similar outcomes have been observed in humans,[12] but randomized trials to determine the true efficacy and long-term safety have not yet been completed. As with PRP, there are multiple other obstacles to mainstream use. The optimal concentration of cells and feasibility of procurement and administration in the office setting will need to be determined, and cost will likely be even more of an issue than for PRP to account for the additional process of cell culturing.

SUMMARY

Master athletes are prone to developing knee OA that can inhibit their participation in sports and exercise. To reduce symptoms, continuation of low-impact, moderately intense exercise should be encouraged. Bracing, taping, orthotics, and physical therapy regimens have demonstrated short-term benefits in specific patient populations. Dietary supplements have negligible impacts. Although oral NSAIDs are inexpensive and effective pain relievers for knee OA, high systemic levels and side effects can be especially troublesome in the elderly. Topical NSAIDs appear to have equivalent efficacy with lower systemic levels. Steroid injections provide relief that typically lasts less than a month, while the benefits of viscosupplementation may not outweigh the risks. Other localized therapies, such as intra-articular injections of botulinum toxin and biologics have shown short-term benefits, but the long-term sequelae are largely unknown and need more research.

REFERENCES

1. American Geriatrics Society Panel on Exercise and Osteoarthritis. Exercise prescription for older adults with osteoarthritis pain: consensus practice recommendations: a supplement to the AGS clinical practice guidelines on the management of chronic pain in older adults. *J Am Geriatr Soc.* 2001;49:808-823.
2. Appelboom T, Schuermans J, Verbruggen G, Henrotin Y, Reginster JY. Symptoms modifying effect of avocado/soybean unsaponifiables (ASU) in knee osteoarthritis: a double blind, prospective, placebo-controlled study. *Scand J Rheumatol.* 2001;30:242-247.
3. Arokoski JP, Jurvelin JS, Väätäinen U, Helminen HJ. Normal and pathological adaptations of articular cartilage to joint loading. *Scand J Med Sci Sports.* 2000;10:186-198.

4. Baker KR, Matthan NR, Lichtenstein AH, et al. Association of plasma n-6 and n-3 polyunsaturated fatty acids with synovitis in the knee: the MOST study. *Osteoarthritis Cartilage.* 2012;20:382-387.
5. Baltzer AW, Moser C, Jansen SA, Krauspe R. Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. *Osteoarthritis Cartilage.* 2009;17:152-160.
6. 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.
7. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev.* 2006;2:CD005321.
8. Birklein F, Schmelz M. Neuropeptides, neurogenic inflammation and complex regional pain syndrome (CRPS). *Neurosci Lett.* 2008;437:199-202.
9. Boon AJ, Smith J, Dahm DL, et al. Efficacy of intra-articular botulinum toxin type A in painful knee osteoarthritis: a pilot study. *PM R.* 2010;2:268-276.
10. Buckwalter JA, Lane NE. Athletics and osteoarthritis. *Am J Sports Med.* 1997;25:873-881.
11. Center of Disease Control and Prevention. Table 73. Participation in leisure-time aerobic and muscle-strengthening activities that meet the 2008 federal physical activity guidelines for adults 18 years of age and over, by selected characteristics: United States, selected years 1998-2010. http://www.cdc.gov/nchs/hus/contents2011.htm#trendtables. Accessed September 7, 2012.
12. Centeno CJ, Busse D, Kisiday J, Keohan C, Freeman M, Karli D. Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells. *Pain Physician.* 2008;11:343-353.
13. Chakravarty EF, Hubert HB, Lingala VB, Zatarain E, Fries JF. Long distance running and knee osteoarthritis: a prospective study. *Am J Prev Med.* 2008;35:133-138.
14. Chen AL, Mears SC, Hawkins RJ. Orthopaedic care of the aging athlete. *J Am Acad Orthop Surg.* 2005;13:407-416.
15. Cheng OT, Souzdalnitski D, Vrooman B, Cheng J. Evidence-based knee injections for the management of arthritis. *Pain Med.* 2012;13:740-753.
16. Chevalier X. Intraarticular treatments for osteoarthritis: new perspectives. *Curr Drug Targets.* 2010;11:546-560.
17. 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.
18. Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med.* 2006;354:795-808.
19. Cress ME, Buchner DM, Questad KA, Esselman PC, deLateur BJ, Schwartz RS. Exercise: effects on physical functional performance in independent older adults. *J Gerontol A Biol Sci Med Sci.* 1999;54:M242-248.
20. De Vries HA. Physiological effects of an exercise training regimen upon men aged 52 to 88. *J Gerontol.* 1970;25:325-336.
21. Dehn MM, Bruce RA. Longitudinal variations in maximal oxygen intake with age and activity. *J Appl Physio.* 1972;33:805-807.
22. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. *Lancet.* 2005;365:965-973.
23. Draganich L, Reider B, Rimington T, Piotrowski G, Mallik K, Nasson S. The effectiveness of self-adjustable custom and off-the-shelf bracing in the treatment of varus gonarthrosis. *J Bone Joint Surg Am.* 2006;88:2645-2652.
24. Everts PA, Brown Mahoney C, Hoffmann JJ, et al. Platelet-rich plasma preparation using three devices: implications for platelet activation and platelet growth factor release. *Growth Factors.* 2006;24:165-171.
25. Felson DT. Does excess weight cause osteoarthritis and, if so, why? *Ann Rheum Dis.* 1996;55:668-670.
26. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women: the Framingham Study. *Ann Intern Med.* 1992;116:535-539.
27. Filardo G, Kon E, Buda R, et al. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. *Knee Surg Sports Traumatol Arthrosc.* 2011;19:528-535.
28. Foster C, Wright G, Battista RA, Porcari JP. Training in the aging athlete. *Curr Sports Med Rep.* 2007;6:200-206.
29. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. *Am J Sports Med.* 2009;37:2259-2272.
30. Fransen M, McConnell S. Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev.* 2008;4:CD004376.
31. Fujimoto N, Prasad A, Hastings JL, et al. Cardiovascular effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age. *Circulation.* 2010;122:1797-1805.
32. Goldring MB, Goldring SR. Osteoarthritis. *J Cell Physiol.* 2007;213:626-634.
33. Goodpaster BH, Park SW, Harris TB, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci.* 2006;61:1059-1064.
34. Griffin TM, Fermor B, Huebner JL, et al. Diet-induced obesity differentially regulates behavioral, biomechanical, and molecular risk factors for osteoarthritis in mice. *Arthritis Res Ther.* 2010;12:R130.
35. Hashikawa T, Osaki M, Ye Z, et al. Factors associated with radiographic osteoarthritis of the knee among community-dwelling Japanese women: the Hizen-Oshima Study. *J Orthop Sci.* 2011;16:51-55.
36. Henriksen M, Christensen R, Danneskiold-Samsøe B, Bliddal H. Changes in lower extremity muscle mass and muscle strength after weight loss in obese patients with knee osteoarthritis: a prospective cohort study. *Arthritis Rheum.* 2012;64:438-442.
37. Hinman RS, Crossley KM, McConnell J, Bennell KL. Efficacy of knee tape in the management of osteoarthritis of the knee: blinded randomised controlled trial. *BMJ.* 2003;327:135.
38. Hootman J, Fitzgerald S, Macera C, Blair SN. Lower extremity muscle strength and risk of self-reported hip or knee osteoarthritis. *J Phys Act Health.* 2004;1:321-330.
39. Howe TE, Shea B, Dawson LJ, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst Rev.* 2011;7:CD000333.
40. Hunter GR, McCarthy JP, Bamman MM. Effects of resistance training on older adults. *Sports Med.* 2004;34:329-348.
41. Hurley MV, Scott DL. Improvements in quadriceps sensorimotor function and disability of patients with knee osteoarthritis following a clinically practicable exercise regime. *Br J Rheumatol.* 1998;37:1181-1187.
42. Issa RI, Griffin TM. Pathobiology of obesity and osteoarthritis: integrating biomechanics and inflammation. *Pathobiol Aging Age Relat Dis.* 2012;2.
43. Jackson DW, Evans NA, Thomas BM. Accuracy of needle placement into the intra-articular space of the knee. *J Bone Joint Surg Am.* 2002;84:1522-1527.
44. Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier JP, Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol.* 2011;7:33-42.
45. Kirkley A, Webster-Bogaert S, Litchfield R, et al. The effect of bracing on varus gonarthrosis. *J Bone Joint Surg Am.* 1999;81:539-548.
46. Komistek RD, Dennis DA, Northcut EJ, Wood A, Parker AW, Traina SM. An in vivo analysis of the effectiveness of the osteoarthritic knee brace during heel-strike of gait. *J Arthroplasty.* 1999;14:738-742.
47. Kon E, Mandelbaum B, Buda R, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. *Arthroscopy.* 2011;27:1490-1501.
48. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: part II. *Arthritis Rheum.* 2008;58:26-35.
49. Leitner GC, Gruber R, Neumüller J, et al. Platelet content and growth factor release in platelet-rich plasma: a comparison of four different systems. *Vox Sang.* 2006;91:135-139.
50. Lucioni A, Bales GT, Lotan TL, McGehee DS, Cook SP, Rapp DE. Botulinum toxin type A inhibits sensory neuropeptide release in rat bladder models of acute injury and chronic inflammation. *BJU Int.* 2008;101:366-370.
51. Mahowald ML, Singh JA, Dykstra D. Long term effects of intraarticular botulinum toxin A for refractory joint pain. *Neurotox Res.* 2006;9:179-188.
52. Malvankar S, Khan WS, Mahapatra A, Dowd GS. How effective are lateral wedge orthotics in treating medial compartment osteoarthritis of the knee? A systematic review of the recent literature. *Open Orthop J.* 2012;6:544-547.
53. McIlwraith CW. The use of intra-articular corticosteroids in the horse: what is known on a scientific basis? *Equine Vet J.* 2010;42:563-571.
54. Messier SP, Gutekunst DJ, Davis C, DeVita P. Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. *Arthritis Rheum.* 2005;52:2026-2032.
55. Mokbel AN, El Tookhy OS, Shamaa AA, Rashed LA, Sabry D, El Sayed AM. Homing and reparative effect of intra-articular injection of autologous mesenchymal stem cells in osteoarthritic animal model. *BMC Musculoskelet Disord.* 2011;12:259.
56. Mokbel AN, El Tookhy OS, Shamaa AA, Sabry D, Rashed LA, Mostafa A. Homing and efficacy of intra-articular injection of autologous mesenchymal stem cells in experimental chondral defects in dogs. *Clin Exp Rheumatol.* 2011;29:275-284.
57. Oliveria SA, Felson DT, Cirillo PA, Reed JI, Walker AM. Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. *Epidemiology.* 1999;10:161-166.

58. Pavelka K, Coste P, Géher P, Krejci G. Efficacy and safety of piascledine 300 versus chondroitin sulfate in a 6 months treatment plus 2 months observation in patients with osteoarthritis of the knee. *Clin Rheumatol.* 2010;29:659-670 [erratum 2010;29:819-820].
59. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch Intern Med.* 2002;162:2113-2123.
60. Pelletier MH, Malhotra A, Brighton T, Walsh WR, Lindeman R. Platelet function and constituents of platelet rich plasma. *Int J Sports Med.* 2013;34:74-80.
61. Peregoy J, Wilder FV. The effects of vitamin C supplementation on incident and progressive knee osteoarthritis: a longitudinal study. *Public Health Nutr.* 2011;14:709-715.
62. Public Health Service Act, 42 USC § 264 (2012).
63. Raynauld JP, Buckland-Wright C, Ward R, et al. Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2003;48:370-377.
64. Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet.* 2001;357:251-256.
65. Reichenbach S, Sterchi R, Scherer M, et al. Meta-analysis: chondroitin for osteoarthritis of the knee or hip. *Ann Intern Med.* 2007;146:580-590.
66. Richmond J, Hunter D, Irrgang J, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on the treatment of osteoarthritis (OA) of the knee. *J Bone Joint Surg Am.* 2010;92:990-993.
67. 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.
68. Rutjes AW, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med.* 2012;157:180-191.
69. Sattelmair JR, Pertman JH, Forman DE. Effects of physical activity on cardiovascular and noncardiovascular outcomes in older adults. *Clin Geriatr Med.* 2009;25:677-702.
70. Segal NA, Glass NA, Torner J, et al. Quadriceps weakness predicts risk for knee joint space narrowing in women in the MOST cohort. *Osteoarthritis Cartilage.* 2010;18:769-775.
71. Segal NA, Torner JC, Felson D, et al. Effect of thigh strength on incident radiographic and symptomatic knee osteoarthritis in a longitudinal cohort. *Arthritis Rheum.* 2009;61:1210-1217.
72. Simon LS, Grierson LM, Naseer Z, Bookman AA, Zev Shainhouse J. Efficacy and safety of topical diclofenac containing dimethyl sulfoxide (DMSO) compared with those of topical placebo, DMSO vehicle and oral diclofenac for knee osteoarthritis. *Pain.* 2009;143:238-245.
73. Singh JA. Botulinum toxin therapy for osteoarticular pain: an evidence-based review. *Ther Adv Musculoskelet Dis.* 2010;2:105-118.
74. Singh JA, Mahowald ML, Noorbaloochi S. Intraarticular botulinum toxin A for refractory painful total knee arthroplasty: a randomized controlled trial. *J Rheumatol.* 2010;37:2377-2386.
75. Singh JA, Mahowald ML, Noorbaloochi S. Intra-articular botulinum toxin A for refractory shoulder pain: a randomized, double-blinded, placebo-controlled trial. *Transl Res.* 2009;153:205-216.
76. Sinusas K. Osteoarthritis: diagnosis and treatment. *Am Fam Physician.* 2012;85:49-56 [erratum 2012;86:893].
77. Sowers M, Lachance L. Vitamins and arthritis: the roles of vitamins A, C, D, and E. *Rheum Dis Clin North Am.* 1999;25:315-332.
78. Spaková T, Rosocha J, Lacko M, Harvanová D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. *Am J Phys Med Rehabil.* 2012;91:411-417.
79. Stanley KL, Weaver JE. Pharmacologic management of pain and inflammation in athletes. *Clin Sports Med.* 1998;17:375-392.
80. Stevenson JD, Roach R. The benefits and barriers to physical activity and lifestyle interventions for osteoarthritis affecting the adult knee. *J Orthop Surg Res.* 2012;7:15.
81. Strand V, Baraf HS, Lavin PT, Lim S, Hosokawa H. A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage.* 2012;20:350-356.
82. Thomas KS, Muir KR, Doherty M, Jones AC, O'Reilly SC, Bassey EJ. Home based exercise programme for knee pain and knee osteoarthritis: randomised controlled trial. *BMJ.* 2002;325:752.
83. Towheed TE. Pennsaid therapy for osteoarthritis of the knee: a systematic review and metaanalysis of randomized controlled trials. *J Rheumatol.* 2006;33:567-573.
84. Towheed T, Maxwell L, Anastassiades TP, et al. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev.* 2005;2:CD002946.
85. Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev.* 2006;1:CD004257.
86. Tugwell PS, Wells GA, Shainhouse JZ. Equivalence study of a topical diclofenac solution (pennsaid) compared with oral diclofenac in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. *J Rheumatol.* 2004;31:2002-2012.
87. Wandel S, Jüni P, Tendal B, et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ.* 2010;341:c4675.
88. Wang BW, Ramey DR, Schettler JD, Hubert HB, Fries JF. Postponed development of disability in elderly runners: a 13-year longitudinal study. *Arch Intern Med.* 2002;162:2285-2294.
89. Wang Y, Davies-Tuck ML, Wluka AE, et al. Dietary fatty acid intake affects the risk of developing bone marrow lesions in healthy middle-aged adults without clinical knee osteoarthritis: a prospective cohort study. *Arthritis Res Ther.* 2009;11:R63.
90. Wang Y, Hodge AM, Wluka AE, et al. Effect of antioxidants on knee cartilage and bone in healthy, middle-aged subjects: a cross-sectional study. *Arthritis Res Ther.* 2007;9:R66.
91. Warden SJ, Hinman RS, Watson MA Jr, Avin KG, Bialocerkowski AE, Crossley KM. Patellar taping and bracing for the treatment of chronic knee pain: a systematic review and meta-analysis. *Arthritis Rheum.* 2008;59:73-83.
92. Wilson B, Rankin H, Barnes CL. Long-term results of an unloader brace in patients with unicompartmental knee osteoarthritis. *Orthopedics.* 2011;34:e334-337.