


Management of the Retired Athlete with Osteoarthritis of the Knee

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Abstract

Purpose: Osteoarthritis of the knee is a complex interaction of biological, mechanical, and biochemical factors that are further complicated by injury, which accelerates pathological processes within the joint. As a result, athletes, particularly those with a history of knee injury, have an earlier onset and higher prevalence of osteoarthritis that would be expected based on their age. This can present a clinical dilemma to the physician managing the patient who, despite the presence of radiologically confirmed disease, has few symptoms and wishes to maintain an active lifestyle. **Methods:** We reviewed meta-analyses and systematic reviews of randomized controlled trials about clinical management of knee osteoarthritis with special interest on effect sizes. **Results:** Numerous management options have undergone the rigor of clinical trials and subsequently have been summarized in meta-analyses and systematic reviews, the results of which offer evidence regarding varying degrees of effect. Based on the available evidence, most summaries and clinical practice guidelines suggest a regimen of patient education, self-management, weight control, and exercise supported by individualized pain management strategies. Other noninvasive or less invasive strategies are available that have varying degrees of effect. **Conclusions:** Although the evidence supporting many of the clinical management options might be considered modest, those effects are sufficient to permit an active lifestyle and have, given the prevalence of the disease, a public health impact.

Keywords

osteoarthritis diagnosis, sports injury diagnosis, knee joint involved, nonsurgical therapy

The issue of osteoarthritis (OA) in the retired athlete can hardly be considered to be a recent development. Although it is hard to trace back to a time when OA was a new observation in athletes, Muckle¹ discussed the “footballer’s meniscus,” which included bucket handle or oblique tears of both meniscal horns that resulted in pain, swelling, and instability with many players showing signs but no symptoms. Injury was frequently associated with damage to the hyaline cartilage; players were delayed in returning to play; and when they did return, their “poor match agility” forced many to decrease their level of play. Importantly, repeat operations were associated with the onset of OA. The players with the worst outcomes were those with a lateral meniscectomy from the dominant leg. Professionals developed OA sooner (3-5 years post surgery) than did amateurs (5-7 years). As the average age of the index injury was 24 years, players displayed evidence of OA earlier than might be expected for their age. Muckle’s comment about the presence of radiographic signs in the absence of clinical symptoms underlines that the clinician’s role is directed at treating the patient’s symptoms, not the underlying disease.

Although the role of injury in the manifestation of knee OA is common knowledge, where athletic activity fits in

the spectrum of risk factors can influence disease management decisions. Risk factors for OA, like most other sports injuries, can be categorized as either modifiable or non-modifiable (**Table 1**). In general, the obese, female African American, with a varus defect of the knee, and who frequently squats or kneels, has a high risk of developing knee OA. The athlete, especially one with a history of a knee injury, who has gained substantial weight after retirement and has not maintained good neuromuscular control of the muscles around the knee, hip, and ankle seems to develop OA at an earlier age than might be expected in the nonathletic population.²⁻⁵

It has been suggested that simply playing soccer may be a contributing factor for knee OA.^{3,6-11} Injury, however, specifically meniscal injury, seems to play a greater role^{4,7,12,13} and may have more influence on management decisions. Athletes cannot change their injury history, but

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Table 1. Risk Factors for Osteoarthritis

Modifiable	Nonmodifiable
Joint trauma	Age
Repetitive overload (mostly occupational or musculoskeletal alignment)	Gender
Obesity	Genetics
Neuromuscular function	Race
Quadriceps weakness	Previous inflammatory joint disease
Nutritional deficits (vitamins D, calcium)	Metabolic or endocrine disorders

Note: Modified from Kelley, 2006.⁵⁷

they can manage their weight as well as strive to maintain optimal muscle function of the lower extremity to minimize the magnitude of the repetitive loads of daily activities and use the muscular system to absorb much of the load to delay, or prevent, the progression of OA. The front line in disease management includes a variety of strategies to support the athlete's ability to continue routine activities.

Harvey and Hunter¹⁴ argued that calling OA a "degenerative joint disease" minimizes the contribution of genetic, biochemical, mechanical, nutritional, and biological factors and that appropriate management of the disease needs to address each factor. Further, Lohmander and colleagues¹³ stated that "osteoarthritis development in the injured joints is caused by intra-articular pathogenic processes initiated at the time of injury, combined with long-term changes in dynamic joint loading." (pg. 1756) The focus of this review will be on systematic reviews and meta-analyses to present effect sizes (Note 1) in order to compare treatment effectiveness on a level playing field. We will outline the management options of OA for the retired athlete with specific focus on education and activity options to maintain and improve neuromuscular function of the lower extremity that will, we hope, modify those changes in dynamic joint loading.

Self-Management Practices

Education and Regular Patient Contact

A first step in managing the retired player with OA is supplying information about the importance of self-management. Players need to know that personal decisions and behaviors will influence how their OA affects their daily activities. Numerous recommendations stress the importance of patient education, consistent with what has been presented by the Arthritis Foundation.¹⁵ The patient who understands the nature of OA, along with the benefits of changes in activity, exercise, and lifestyle modification, can realize a significant reduction in pain, even though the effect is not large. Recent reviews¹⁶⁻¹⁸ indicate that at low cost with few adverse effects, the well-informed patient makes more positive decisions

regarding lifestyle. In addition, regular contact from the health care provider's office aids in compliance, and therefore the patient experiences less pain. What specific individual aspect of a comprehensive self-management program produces the greatest effect is unknown. Regardless, that a small effect on a large fraction of the population should have a public health impact at a low cost or risk argues in favor of the central role of patients in the management of their disease.

Reduction in Body Mass

Given the interaction of regular physical training and caloric intake, athletes have an advantage when it comes to weight maintenance. Once they retire or reduce their commitment to their sport, however, many athletes fail to reduce caloric intake and thus gain body mass. For example, some of the leanest players in the National Football League (defensive backs and receivers) gain an average of 15 to 20 pounds in retirement (Marshall and Guskiewicz, 2011; personal communication). An increase in mass is known to increase loads on weightbearing joints, which likely exacerbates the development of OA through mechanical and metabolic means.¹⁹ In addition, a high-fat diet leading to obesity (in mice) has been shown to induce osteoarthritic changes in the knee as well as decreased motor performance and selected behavior traits.²⁰ Patients who are overweight (body mass index >25) should be counseled to lose a minimum of 5% of their body mass through appropriate exercise and dietary modification; each unit reduction in body mass reduces load by 4 units.²¹ This goes along with other well-known health benefits of similar weight loss.

Exercise

The exercise options available to the OA patient are somewhat limited because many options overload the knee to the point of increased pain and reduced function. Thus, only 30% of patients with early OA (Kellgren-Lawrence grade II or less; i.e., no joint space narrowing) meet U.S. Centers for Disease Control and Prevention or American College of Sports Medicine recommendations for daily physical activity,

Table 2. Exercise Prescription for Adults with Osteoarthritis

Type	Intensity	Volume	Frequency
Static stretching, initial	To sensation of resistance	1 per muscle group, up to 15 s each	Daily
Flexibility, long term	Through full range of motion	Up to 5 per muscle group; up to 30 s each	3-5/wk
Strengthening	Low intensity: 40% of 1 RM	10-15 repetitions	2-3/wk
	Moderate intensity: 40-60% of 1 RM	8-10 repetitions	2-3/wk
	High intensity: >60% of 1 RM	6-8 repetitions	2-3/wk
Aerobic, low impact	40-60% of capacity ("light" to "somewhat hard" exertion)	Totalling 20-30 min/d	2-5/wk

Note: Modified from the American Geriatrics Society, 2001.³⁵ RM = repetition maximum.

and only 1% perform any vigorous physical activity (>6.0 metabolic equivalents).²²

In vitro cartilage health is dependent on compression from cyclic, dynamic loading, properties of which are closely coupled with cartilage biology that increases chondrocyte anabolism as well as extracellular matrix components.²³ In vivo, moderate exercise also has an anabolic effect on cartilage. In older individuals, however, the loading from high-intensity exercise (or sudden onset of exercise or immobilization) can lead to degenerative changes in the collagen network.²⁴

Injury does not affect just the meniscus or articular cartilage. After rehabilitation from a knee injury, it is not unusual for the patient's injured extremity to have enduring muscle weakness (frequently out of proportion to the loss of muscle mass,²⁵ suggestive of some manner of inhibition), reduced range of motion, and diminished proprioception that may continue to be evident years later. Weak quadriceps are deficient in their shock attenuation capabilities, transmitting loads across the knee at higher rates and magnitudes that effectively alter normal knee mechanics,²⁶ which could be a factor in accelerating the progression of OA on damaged tissues.²⁷ But the simple concept of exercise per se playing a role in the development of OA does not appear to be true, as there are no differences in the rate or radiographic evidence of OA after 2 decades of habitual running by middle-aged runners.²⁸

There is ample evidence that the strength of the thigh musculature in patients with OA can be improved,²⁹ but whether this results in greater muscle cross-sectional area, improved activation patterns, or slowed disease progression is unknown.³⁰ Although increasing the relative strength of the thigh muscles does appear to reduce the risk of developing OA in women, this has not been the case in men.³¹ Further, evidence that increasing muscle strength will protect against OA in those with established OA is lacking. Despite muscle weakness being a factor in OA development, evidence supporting the benefits of increasing muscle strength is not compelling, possibly because of

subject selection (e.g., patients with knee malalignment) or definition (slowed progression verified by radiographs). Regardless, it seems reasonable to speculate that the contributory mechanical factors of posttraumatic OA include persistent weakness, muscle inhibition, and the resulting joint instability. If this arthrogenic muscle inhibition (an inability to achieve full, voluntary activation of the quadriceps)²⁷ could be corrected, the progression toward OA might be retarded.

Although testing of this specific hypothesis continues to evolve, clinical trials on various aspects of exercise consistently report small to moderate effect sizes demonstrating that improvements in selected fitness factors do indeed reduce pain (a known factor in muscle activation) and improve function.^{29,30,32,33} Aerobic exercises like walking may only produce small to moderate effects in pain reduction and disability, but walking also leads to consistent moderate to large effects in the global assessment of benefit.³⁴

The systematic review by Roddy and colleagues³³ presents specific exercise recommendations based on evidence from the literature. They suggest an individualized program of strength and low-impact aerobic training to reduce pain and improve function and overall health that can be done individually or in a group setting and is based on patient-specific factors (e.g., age, comorbidities). Any program needs to be supported with education and feedback to promote a healthy lifestyle and maintain compliance.

These recommendations form the foundation of the Arthritis Foundation's "Moving Is the Best Medicine" initiative. The American Geriatrics Society has produced an exercise prescription specifically for adults with OA pain that emphasizes flexibility, strengthening, and aerobic exercise (**Table 2**).³⁵ Despite the lack of convincing evidence surrounding the mechanisms behind reductions in pain and disability, clinical trials of these protocols consistently demonstrate practical improvement by the patient, and therefore they should be considered as primary treatment modalities.³⁶

Medical Management

Analgesics

The primary goal of using analgesics is pain reduction to improve function and lessen disability. Targets for medications range from cellular components and cytokines to larger objectives like bone, cartilage, neurons, and the vascular supply.

The most common analgesic for mild to moderate pain is acetaminophen. For many, it is the first treatment option for pain relief; having only analgesic properties, acetaminophen is for pain reduction only. It has no impact on the underlying disease. In patients with symptomatic OA, the effect size for pain reduction in placebo-controlled trials has been stable at around 0.14 with no significant effects on stiffness or physical function.³⁷ Because of toxic metabolites, caution is necessary for the patient with kidney or liver disease as well as for patients who ingest even moderate quantities of alcohol. In general, however, standard doses (up to 4 g/d) are well tolerated with few side effects.

The anti-inflammatory and analgesic effects of nonsteroidal anti-inflammatory drugs (NSAIDs) reduce pain with an effect size reported to be 0.29 in placebo-controlled trials³⁸ and 0.20 compared with acetaminophen,³⁹ despite having no modifying effect on the underlying disease.⁴⁰ NSAIDs are, however, linked to gastrointestinal side effects that are worse when NSAIDs are combined with high doses of acetaminophen.⁴¹

Topical NSAIDs have been recommended for symptomatic OA, and although the published effect size of 0.44 argues in favor of their use, there is the possibility of a publication bias with an underreporting of negative results.^{18,42} Topicals continue as a viable treatment option for pain relief because they are as effective as oral NSAIDs and possibly safer.⁴³

Opioids

Should acetaminophen or NSAIDs be ineffective for pain relief, opioids are typically the next treatment option, and the reported effect size of 0.78 indicates that these medications produce significant pain relief but less improvement in physical function (effect size = 0.31).⁴⁴ An effect size of this magnitude for pain reduction needs to be tempered because up to 25% of patients enrolled in trials of opioids voluntarily withdraw, leaving the remaining results as examples of a best-case scenario; in addition, opioids have a wide range of side effects.

Glucosamine and Chondroitin

Glucosamine is a component of joint cartilage and chondroitin sulfate that provides much of cartilage's resistance

to compression. The results of numerous clinical trials indicate that the effect size for glucosamine or chondroitin supplementation on pain relief is 0.46 and 0.79, respectively, but when only the highest quality trials are considered, these values fall to 0.29 and 0.005, respectively.¹⁸ In addition, there are questions of publication bias, blinding, and relationships with funding sources. There has been a steady decline in the effect sizes and narrowing of the confidence intervals for both glucosamine (since 1981, from 2.24 to 0.58) and chondroitin (since 1996, from 1.4 to 0.75).¹⁸ When only the highest quality studies are considered, the overall effect of glucosamine is modest and chondroitin has little benefit for the OA patient.

Acupuncture

The quest for pain relief and improved quality of life may lead a patient to inquire about acupuncture. To date, 11 randomized trials have compared acupuncture versus sham treatments, routine care, and patients on waiting lists. Trials comparing patients versus controls show a reasonable effect size of 0.58 for pain relief⁴⁵ that decreases to 0.35 when compared with sham acupuncture and diminishes further over time (0.13 after 6 months).^{18,45} Thus, although acupuncture might be a reasonable option for short-term pain relief, the data do not support long-term use.

Other Management Options

A number of other options have been investigated with varying degrees of methodological rigor and have shown varying degrees of success but might be considered for selected patients.⁴⁶ For example, patients with varus or valgus knee malalignment might be treated with specific braces. Patients with high loads on the medial compartment can be prescribed lateral heel wedges. Patellar taping, range of motion exercises, flexibility, and free-floating positional devices have been studied, but the results are mostly inconclusive (bracing) or devices have not been recommended (heel wedges, free-floating devices). Those devices recommended by the American Academy of Orthopaedic Surgeons are low cost, low harm, and low level of evidence (range of motion, flexibility) or appear to be effective in the short term (taping), but the studies on which these recommendation are based have design issues.⁴⁶

Injection Therapy

Corticosteroids

Intra-articular injection of corticosteroids for short-term pain relief in the OA patient is a therapeutic option with a long history of reliable data to support its use for rapid, if

Table 3. Summary of Effect Sizes, Evidence Level, Evidence Strength, and AAOS Recommendation for Management of Osteoarthritis Pain

Management Option	Effect size (95% CI)	Level of evidence	Strength of recommendation	AAOS recommended?
Corticosteroid injections	0.58 (0.34 to 0.75)	II	B	Yes
Aerobic exercise	0.52 (0.34 to 0.70)	I	A	Yes
Strengthening	0.32 (0.23 to 0.42)	II	B	Yes
NSAIDs	0.29 (0.22 to 0.35)	II	B	Yes
Weight reduction	0.20 (0.00 to 0.39)	I	A	Yes
Acetaminophen	0.14 (0.05 to 0.22)	II	A	Yes
Regular contact	0.12 (0.00 to 0.24)	I	A	Yes
Education	0.06 (0.03 to 0.10)	II	A	Yes
Self-management	0.06 (0.02 to 0.20)	II	A	Yes
Chondroitin	0.75 (0.50 to 1.01)	I	A	No
Glucosamine	0.58 (0.30 to 0.87)	I	A	No
Lavage/debridement	0.21 (-0.12 to 0.54)	I	A-B	No
Viscosupplementation	0.60 (0.37 to 0.83)	I	A	Inconclusive
Acupuncture	0.35 (0.15 to 0.55)	I	A	Inconclusive
Opioids	0.78 (0.59 to 0.98)	I	A	Not stated

Note: Table modified from Zhang et al.¹⁸ (effect sizes) and Richmond et al.⁴³ (evidence level, strength, and AAOS recommendation). AAOS = American Academy of Orthopaedic Surgeons; CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug.

somewhat brief, pain relief. The pain relief from a single injection of corticosteroids is considerable in the first week, with an effect size of 0.72, but this falls to 0.28 by 4 weeks and 0.21 by 6 weeks.⁴⁷ In the short term, the effect size for pain relief in knees injected every 3 months for 2 years was 0.67 after the first year but only 0.25 after the second year. In addition, corticosteroids have little effect on stiffness or physical function.⁴⁷

Viscosupplementation

Intra-articular injections of hyaluronic acid (HA) to treat OA have become an option for patients in need of a treatment beyond routine exercise and analgesics but not requiring, or wanting, surgical intervention. Hyaluronan is one of the chief components of the extracellular matrix, contributes to cell proliferation and migration, coats each cell, and contributes to the tissue's resistance to compression. It is thought that when HA is injected, it supplements the viscosity of the joint fluid and lubricates and cushions the joint, producing an analgesic effect.

Bellamy and coworkers⁴⁸ reported effect sizes (vs. placebo) between 0.54 and 0.61 for pain relief, improvement in physical function, and reduction in stiffness but reported issues regarding publication bias and significant heterogeneity when comparing the higher molecular weight hylan with the lower molecular weight HA.¹⁸ For example, the meta-analysis by Reichenbach and colleagues⁴⁹ showed that when very strict controls were in place (e.g., blinding, concealment), the effect size for pain control approached zero. When compared with corticosteroids, in the first 4 weeks, there is little difference in pain reduction or a slight early advantage for corticosteroids vs. intraarticular injections of hyaluronic acid.

Platelet-Rich Plasma

Platelet-rich plasma (PRP) and other products that contain platelet-derived growth factors are bioactive components of whole blood that is injected into tissue with poor healing potential or sometimes as an intra-operative "gel." Since the 1970s, the basic science literature has reported on whether PRP augments tissue regeneration through recruitment, proliferation, and differentiation of involved cells, showing median benefit duration of about 9 months in patients with knee OA.⁵⁰ Foster et al.⁵¹ pointed out that the most reports are Level 4 case series, that basic science research still needs to define the many details regarding the cellular mechanisms of action, that current trials are statistically underpowered, and that study designs need to be carefully considered. PRP may be a significant new therapy for treating sports injuries in the future, "but there remains a significant amount of work before this becomes the standard of care." (pg. 2271)

Surgical Interventions

Lavage and Debridement

Should nonsurgical management therapies prove ineffective, surgical intervention is considered. A full treatment of surgery is beyond the scope of this paper, and specific options are dealt with elsewhere in this supplement.

In 2002, Moseley et al.⁵² reported the first randomized trial of arthroscopic procedures (debridement, lavage, sham) in a group of patients with knee OA and reported no group differences for pain or any other secondary pain or function variables. Whether the same results would be evident in patients with preexisting OA and new mechanical symptoms is unknown. Later systematic reviews showed

little to no improvement in joint symptoms from lavage and irrigation.^{53,54}

High Tibial Osteotomy and Arthroplasty

A number of studies of high tibial osteotomy (HTO) have been reviewed by the Cochrane Collaboration. The variability in surgical procedures, data collection, and reporting made any pooling of outcomes problematic. Nonetheless, the authors concluded there was “silver”-level evidence that valgus HTO is effective at reducing pain and improving function⁵⁵ while also allowing patients to return to preoperative activity frequency and duration, albeit with some modification and activity selection.⁵⁶ When unicompartmental arthroplasty and total knee arthroplasty are each compared with HTO, all 3 procedures improve function, with the unilateral procedure leading to fewer postoperative complications and a lower revision rate versus HTO.

In summary, competitive sports, especially at an elite level, may increase the risk of OA, and it is not unusual for many athletes to have a higher grade of OA than would be expected for their age. Although many athletes have signs of OA, many have fewer symptoms than would be expected based on their level of radiologic disease. This may reflect the fact that their history of skilled neuromuscular function consistent with their sport activity can protect them from symptom-based limitations in their daily activities. The available evidence for managing OA in these patients, especially those who wish to continue with some level of activity, suggests that self-management, including moderate low-impact exercise, (Table 3) is effective at controlling pain and improving function. Exercise per se does not appear to accelerate the development of knee OA, and the mere presence of OA does not affect disability. Obesity, knee trauma, occupational stresses, or malalignment, however, will increase the risk of OA. Appropriate measures are effective in staying active and managing pain.

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Note

1. Effect size is a descriptive measure of the strength of a treatment effect. Originating in the social sciences, it is commonly used in meta-analyses to summarize data from multiple studies. Social scientists sometimes categorize effect sizes as small (0.2-0.3), moderate (around 0.5), and large (≥ 0.8).

References

1. Muckle DS. Factors affecting the prognosis of meniscectomy in soccer players. *Br J Sports Med.* 1983;17:88-90.
2. Anderson CL. High rate of osteoarthritis of the knee in former soccer players. *Med Sci Sports Exerc.* 1986;18:141.
3. Chantraine A. Knee joint in soccer players: osteoarthritis and axis deviation. *Med Sci Sports Exerc.* 1985;17:434-9.
4. Feller J. Anterior cruciate ligament rupture: is osteoarthritis inevitable? *Br J Sports Med.* 2004;38:383-4.
5. Golightly YM, Marshall SW, Callahan LF, Guskiewicz K. Early-onset arthritis in retired National Football League players. *J Phys Act Health.* 2009;6:638-43.
6. Drawer S, Fuller CW. Propensity for osteoarthritis and lower limb joint pain in retired professional soccer players. *Br J Sports Med.* 2001;35:402-8.
7. Elleuch MH, Guermazi M, Mezghanni M, Ghroubi S, Fki H, Mefteh S, *et al.* Knee osteoarthritis in 50 former top-level soccer players: a comparative study. *Ann Readapt Med Phys.* 2008;51:174-8.
8. Kujala UM, Kettunen J, Paananen H, Aalto T, Mattie MC, Impivaara O, *et al.* Knee osteoarthritis in former runners, soccer players, weight lifters, and shooters. *Arthritis Rheum.* 1995;38:539-46.
9. Neyret P, Donell ST, DeJour D, DeJour H. Partial meniscectomy and anterior cruciate ligament rupture in soccer players: a study with a minimum 20-year followup. *Am J Sports Med.* 1993;21:455-60.
10. Roos H. Are there long-term sequelae from soccer? *Clin Sports Med.* 1998;17:819-31.
11. Roos H, Lindberg H, Gardsell P, Lohmander LS, Wingstrand H. The prevalence of gonarthrosis and its relation to meniscectomy in former soccer players. *Am J Sports Med.* 1994;22:219-22.
12. Ichiba A, Kishimoto I. Effects of articular cartilage and meniscus injuries at the time of surgery on osteoarthritic changes after anterior cruciate ligament reconstruction in patients under 40 years old. *Arch Orthop Trauma Surg.* 2009;129:409-15.
13. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. *Am J Sports Med.* 2007;35:1756-69.
14. Harvey WF, Hunter DJ. The role of analgesics and intra-articular injections in disease management. *Rheum Dis Clin N Am.* 2008;34:777-88.
15. Arthritis Foundation. Osteoarthritis: the basics about this disease that affects 27 million Americans. 2011. Available from: <http://www.arthritis.org/osteoarthritis.php>. Accessed 23 January 2011.
16. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden NK, *et al.* OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage.* 2007;15:981-1000.

17. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden NK, *et al.* OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage.* 2008;16:137-62.
18. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, *et al.* OARSI recommendations for the management of hip and knee osteoarthritis, part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage.* 2010;18:476-99.
19. Velasquez MT, Katz JD. Osteoarthritis: another component of metabolic syndrome. *Metab Syndr Relat Disord.* 2010;8:295-305.
20. Griffin TM, Fermor B, Huebner JL, Draus VB, Rodriguiz RM, Wetsel WC, *et al.* Diet-induced obesity differentially regulates behavioral, biomechanical, and molecular risk factors for osteoarthritis in mice. *Arthritis Res Ther.* 2010;12:R130.
21. 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;52:2026-32.
22. Farr JN, Going SB, Lohman TG, *et al.* Physical activity levels in patients with early knee osteoarthritis measured by accelerometry. *Arthritis Rheum.* 2008;59:1229-36.
23. Guilak F, Sah RL, Setton LA. Physical regulation of cartilage metabolism. In: Mow VC, Hayes WC, editors. *Basic orthopaedic biomechanics.* Philadelphia: Lippincott-Raven; 1997.
24. Arokoski JP, Jurvelin JS, Vaatainen U, Helminen HJ. Normal and pathological adaptations of articular cartilage to joint loading. *Scand J Med Sci Sports.* 2000;10:186-98.
25. Slemenda C, Brandt KD, Heilman DK, Mazzuca S, Braunstein EM, Katz BP, *et al.* Quadriceps weakness and osteoarthritis of the knee. *Ann Intern Med.* 1997;127:97-104.
26. Brandt KD. Putting muscle into osteoarthritis. *Ann Intern Med.* 1997;127:154-5.
27. Palmieri-Smith RM, Thomas AC. A neuromuscular mechanism of posttraumatic osteoarthritis associated with ACL injury. *Exerc Sports Sci Rev.* 2009;37:147-53.
28. Chakravarty EF, Hubert HB, Lingala VB, Zatarain E, Fries JF. Long distance running and knee osteoarthritis: a prospective study. *Am J Prev Med.* 2008;35:133-8.
29. Pelland L, Brosseau L, Wells G, MacLeay L, Lambert J, Lamothe C, *et al.* Efficacy of strengthening exercises for osteoarthritis (part I): a meta-analysis. *Phys Ther Rev.* 2004;9:77-108.
30. Bennell KL, Hunt MA, Wrigley TV, Boon-Whatt L, Hinman RS. Role of muscle in the genesis and management of knee osteoarthritis. *Rheum Dis Clin North Am.* 2008;34:731-54.
31. 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;1:321-30.
32. Bennell KL, Hinman RS. A review of the clinical evidence for exercise in osteoarthritis of the hip and knee. *J Sci Med Sport.* 2010;14:4-9.
33. Roddy E, Zhang W, Doherty M, Arden NK, Barlow JH, Birrell F, *et al.* Evidence-based recommendations for the role of exercise in the management of osteoarthritis of the hip or knee—the MOVE consensus. *Rheumatology.* 2005;44:67-73.
34. Petrella RJ. Is exercise effective treatment for osteoarthritis of the knee? *Br J Sports Med.* 2000;34:326-31.
35. American Geriatrics Society. 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;49:808-23.
36. Bosomworth NJ. Exercise and knee osteoarthritis: benefit or hazard? *Can Fam Physician.* 2009;55:871-8.
37. Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev.* 2006;(1):CD004257.
38. Bjordal JM, Klovning A, Ljunngren AE, Slordal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: a meta-analysis of randomised placebo-controlled trials. *Eur J Pain.* 2007;11:125-38.
39. Zhang W, Jones A, Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis?: a meta-analysis of randomised controlled trials. *Ann Rheum Dis.* 2004;63:901-7.
40. Stanley KL, Weaver JE. Pharmacologic management of pain and inflammation in athletes. *Clin Sports Med.* 1998;17:375-92.
41. Rahme E, Barkun A, Nedjar H, Gaugris S, Watson D. Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. *Am J Gastroenterol.* 2008;103:872-82.
42. Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. *BMJ.* doi:10.1136/bmj.38159.639028.7C.
43. 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;10:2002-12.
44. Avouac J, Gossec L, Dougados M. Efficacy and safety of opioids for osteoarthritis: a meta-analysis of randomized controlled trials. *Osteoarthritis Cartilage.* 2007;15:957-65.
45. Manheimer E, Linde K, Lao L, Bouter LM, Berman BM. Metaanalysis: acupuncture for osteoarthritis of the knee. *Ann Intern Med.* 2007;146:868-77.
46. Richmond J, Hunter DJ, Irrgang J, Jones MH, Levy B, Marx RG, *et al.* Treatment of osteoarthritis of the knee (nonarthroplasty). *JAAOS.* 2009;17:591-600.
47. 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.
48. 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;CD005321.

49. Reichenbach S, Blank S, Rutjes AW, Shang A, King EA, Dieppe PA, *et al.* Hylan versus hyaluronic acid for osteoarthritis of the knee: a systematic review and meta-analysis. *Arthritis Rheum.* 2007;57:1410-8.
50. Filardo G, Kon E, Buda R, Timoncini A, Di Martino A, Cenacchi A, *et al.* Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. *Knee Surg Sports Traumatol Arthrosc.* 2010. doi:10.1007/s00167-010-1238-6.
51. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. *Am J Sports Med.* 2009;37:2259-72.
52. Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med.* 2002;347:81-8.
53. Arden NK, Reading IC, Jordan KM, Thomas L, Platten H, Hassan A. A randomised controlled trial of tidal irrigation vs corticosteroid injection in knee osteoarthritis: the KIVIS study. *Osteoarthritis Cartilage.* 2008;16:733-9.
54. Laupattarakasem W, Laopaiboon M, Laupattarakasem P, Sumananont C. Arthroscopic debridement for knee osteoarthritis. *Cochrane Database Syst Rev.* 2008;CD005118.
55. Brouwer RW, van Raaij TM, Bierma-Zeinstra SM, Verhagen AP, Jakma TS, Verhaar JA. Osteotomy for treating knee osteoarthritis. *Cochrane Database Syst Rev.* 2007;CD004019.
56. Salzmann GM, Ahrens P, Naal FD, El-Azab H, Spang TJ, Imhoff AB, *et al.* Sporting activity after high tibial osteotomy for the treatment of medial compartment knee osteoarthritis. *Am J Sports Med.* 2009;37:312-8.
57. Kelley LMT. Nonsurgical management of osteoarthritis of the knee. *JAAPA.* 2006;19:26-32.