World Journal of Clinical Cases

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DOI: 10.12998/wjcc.v3.i2.89

World J Clin Cases 2015 February 16; 3(2): 89-101
ISSN 2307-8960 (online)

REVIEW

State-of-the-Art management of knee osteoarthritis

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Received: June 30, 2014
Peer-review started: June 30, 2014
First decision: September 16, 2014
Revised: September 29, 2014
Accepted: October 28, 2014
Article in press: October 29, 2014
Published online: February 16, 2015

Abstract

Osteoarthritis (OA) is the most common type of arthritis found in the United States' population and is also the most common disease of joints in adults throughout the world with the knee being the most frequently affected of all joints. As the United States' population ages along with the increasing trends in obesity prevalence in other parts of the world, it is expected that the burden of OA on the population, healthcare system, and overall economy will continue to increase in the future without making major improvements in managing knee OA. Numerous therapies aim to reduce symptoms of knee OA and continued research has helped to further understand the complex pathophysiology of its disease mechanism attempting to uncover new potential targets for the treatment of OA. This review article seeks to evaluate the current practices for managing knee OA and discusses emerging therapies on the horizon. These practices include non-pharmacological treatments such as providing patient education and self-management strategies, advising weight loss, strengthening programs, and addressing biomechanical issues with bracing or foot orthoses. Oral analgesics and anti-inflammatories are pharmacologicals that are commonly used and the literature overall supports that some of these medications can be helpful for managing knee OA in the short-term but are less effective for long-term management. Additionally, more prolonged use significantly increases the risk of serious associated side effects that are not too uncommon. Disease-modifying osteoarthritis drugs are being researched as a treatment modality to potentially halt or slow disease progression but data at this time is limited and continued studies are being conducted to further investigate their effectiveness. Intra-articular injectables are also implemented to manage knee OA ranging from corticosteroids to hyaluronans to more recently platelet-rich plasma and even stem cells while several other injection therapies are presently being studied. The goal of developing new treatment strategies for knee OA is to prolong the need for total knee arthroplasty which should be utilized only if other strategies have failed. High tibial osteotomy and unicompartmental knee arthroplasty are potential alternatives if only a single compartment is involved with more data supporting unicompartmental knee arthroplasty as a good treatment option in this scenario. Arthroscopy has been commonly used for many years to treat knee OA to address degenerative articular cartilage and menisci, however, several high-quality studies have shown that it is not a very effective treatment for the majority of cases and should generally not be considered when managing knee OA. Improving the management of knee OA requires a multi-faceted treatment approach along with continuing to broaden our understanding of this

complex disease so that therapeutic advancements can continue to be developed with the goal of preventing further disease progression and even potentially reversing the degenerative process.

Key words: Disease-modifying osteoarthritis drugs; Knee osteoarthritis; Disease-modifying osteoarthritis drugs; Osteoarthritis management; Non-steroidal anti-inflammatory drugs; Hyaluronic acid; Arthroscopy; Platelet-rich plasma; Corticosteroids; Stem cells

Core tip: The management of knee osteoarthritis is of growing importance in the world and especially in the United States where an aging population and increasing trends in obesity are increasing the prevalence of this disease. Treatment has traditionally focused on symptom control, however, more recently there has been a greater emphasis placed on developing new modalities that aim to slow disease progression or even reverse the process. This review aims to examine the available literature on such modalities ranging from patient education and weight loss to disease-modifying osteoarthritis drugs to platelet-rich plasma, stem cells, and other emerging injectables.

Fibel KH, Hillstrom HJ, Halpern BC. State-of-the-Art management of knee osteoarthritis. *World J Clin Cases* 2015; 3(2): 89-101 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i2/89.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i2.89

INTRODUCTION

Osteoarthritis (OA) is the most common type of arthritis found in the United States population and is also the most common disease of joints in adults throughout the world[1,2]. The knee joint is the most frequently affected of all joints per epidemiological studies with estimates of 37% of United States' adults ⩾ 60 years of age having radiographic evidence of knee OA and 12% having symptoms related to knee OA accompanying radiographic findings[3]. Osteoarthritis risk factors include both genetic and environmental components with multivariable analysis showing significantly higher odds of symptomatic and radiographic knee OA with body mass index ⩾ 30, greater age, non-Hispanic Black race/ethnicity, and among men with manual labor occupations[2,3]. Symptomatic knee OA has also been highly associated with self-reported activity limitations, need for assistive walking devices, and increased use of prescription medications for pain relief[3]. With an aging United States' population and increasing trends in obesity prevalence, it can be expected that the burden of OA on the population, healthcare system, and overall economy will continue to increase in the future without major improvements in management of knee OA. While the synovium, bone, and cartilage are recognized as the main structures being destroyed during disease progression, further research in the field is revealing that OA is not simply a biomechanical process placing excess load on the affected joint but contributions from catabolic cytokine cascades and production of inflammatory mediators also play a significant role and should be targets for intervention[4,5]. In order to take necessary strides towards improving management of knee OA, it is crucial to recognize the complex pathophysiology of its disease mechanism in which a multi-faceted treatment strategy should be employed using both non-pharmacological and pharmacological options, along with understanding the role for surgical intervention. While numerous treatments aim to offer pain relief to better tolerate the symptoms of knee OA, other modalities are attempting to slow the disease progression, halt it, or even reverse it by trying to affect the damaged articular cartilage. Various treatment strategies, both commonly used and newer advances, for the management of knee OA will be reviewed in this present article focusing mainly on non-operative treatments.

NON-OPERATIVE MANAGEMENT

Non-pharmacological

Education and self-management: Multiple societal guidelines and expert panels recognize patient education and self-management strategies as important components of knee OA management[6]. A systematic review and meta-analysis in 2011 evaluated the effectiveness of self-management programs on pain and disability for chronic musculoskeletal pain in which small to moderate effects in improving pain and disability at the long-term level were found using self-management programs[7]. Recent randomized clinical trials have also highlighted benefits from education and self-management, specifically Ravaud *et al*[8] showed that goal-oriented visits focusing on education on OA and treatment management, information on physical exercises, and information on weight loss led to improvement in weight loss and time spent on physical activity[8,9]. These programs can play more significant roles when implemented in conjunction with weight loss and exercise programs by increasing adherence.

Weight loss and strengthening

While genetic and other endogenous risk factors can contribute to knee OA and its progression, it is important to recognize the negative effects that increased stress on the knee joint can have

in the development and progression of OA. Both weight gain and decreased strength of surrounding musculature can increase the load seen by the knee. With the average body weight of the US population increasing across all ages but more significantly in adult population and this being an issue in other parts of the world, weight loss should be addressed as part of the management of knee OA. The Framingham Study by Felson *et al*[10] demonstrated that women with an approximately 5 kg weight loss had a 50% reduction in the risk of development of symptomatic knee OA. Christensen *et al*[11] used a meta-regression analysis of randomized controlled trials to evaluate if there were changes in pain and function when overweight patients with knee OA achieve a weight loss. The study concluded that disability could be significantly improved when weight was reduced > 5.1% over a 20-wk period, or at the rate of > 0.24% reduction per week[11]. Conversely, Riddle *et al*[12] found there to be a significant dose-response relationship between the extent of percentage change in body weight and the extent of change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function and WOMAC pain scores, specifically those who gained ⩾ 10% of body weight had worse WOMAC physical function score. Not only has weight change been shown to affect pain and function, it has also been associated with MRI changes as Teichtahl *et al*[13] showed that obese individuals with OA who lost as little as 1% of their body weight were able to reduce the amount of medial femorotibial cartilage volume loss. The relationship between obesity, muscle strength, activity level, and knee OA is complex and it can be difficult to determine which factor is contributing most to the disease. While some studies have suggested that people engaging in relatively high levels of activity have an increased risk of developing knee OA compared to sedentary people, other studies have shown a protective effect. Regarding those who have already developed knee OA, a 2011 systematic review demonstrated moderate effect of strength training and exercise in reducing pain and improved physical function significantly. Furthermore, a 2013 meta-analysis including 60 trials showed that an approach combining exercises to increase strength, flexibility, and aerobic capacity was the most effective in managing lower limb OA with trials largely of patients with knee OA[14]. However, another systematic review and meta-analysis in 2014 included 48 randomized controlled trials and found similar effects in reducing pain from knee OA with aerobic, resistance, and performance exercise. In contrast to the 2013 meta-analysis, it concluded that optimal exercise programs for knee OA should have one aim and focus on improving aerobic capacity, quadriceps muscle strength, or lower extremity performance rather than combining the exercises. While both of these analyses demonstrate a positive effect of exercises on knee OA, the most beneficial regimen is still debatable[15]. The IDEA Randomized Clinical Trial included 3 groups in which participants either were involved with intensive weight loss (⩾ 10% body weight), exercise (1 h for 3 d/wk), or both. After this 18 mo randomized control trial, WOMAC pain scores were reduced to no or little pain in 20% in the weight loss only group, 22% in the exercise only group, and 40% in the weight loss and exercise group[16]. This further supports the notion that both weight loss and exercise are important in managing knee OA as they are more effective in combination than either one alone.

Biomechanical interventions (knee braces, knee sleeves, foot orthoses)

Using an appropriate specialist, assessment of biomechanics and incorporating corrective devices may be an effective intervention for knee OA. A key concept in understanding potential benefit from foot orthoses and knee bracing is in relation to the knee adduction moment (KAM) during gait in which excessive KAM has been associated with radiographic knee OA severity, radiographic knee OA progression, and pain with knee OA[17-19]. However, Zifchock *et al*[20] contended that medial joint space and peak adduction angle, not peak adduction moment, were the best predictors of knee pain. A systematic analysis on the effectiveness of knee braces and foot orthoses in conservative management of knee OA produced results suggesting that knee brace and foot orthoses are an effective means of decreasing pain, joint stiffness, and use of pain medication with minimal adverse effects[21]. However, the authors recognized that conclusions of this systematic analysis were limited due to poor quality of trials and heterogeneity of interventions. Lateral wedge insoles, also designed to reduce KAM and therefore decrease medial knee joint loading, have shown mixed results in studies with some claiming no benefit and others arguing its use as an alternative to valgus bracing for medial knee OA[22,23]. A benefit was well demonstrated in a retrospective study of 51 older adults with mild-to-severe medial knee OA in which a significant reduction in pain and improvements in function and quality of life were found with the prescription of a custom-made lateral wedge insole with arch support[24]. With regards to knee OA bracing, it is designed to create either valgus or varus force to alter the contact pressures especially with unicompartmental knee OA. A Cochrane review of orthoses for knee OA included 4 trials in which 1 investigated effectiveness of a knee brace while 3 examined foot orthoses[25]. The study on knee bracing compared a medial compartment unloader brace group, a neoprene sleeve group, and to a control

group in those that had varus deformity of the knee. Both the brace and sleeve group demonstrated significant improvement in disease specific quality of life and function compared to the control group with the brace group also demonstrating statistically significant improvement compared to the sleeve group per WOMAC pain scores[26]. The three studies on orthoses in the Cochrane review were able to conclude that there is some, though limited, evidence that a laterally wedged insole decreases non-steroidal anti-inflammatory drug intake compared with a neutral insole, patient compliance is better in the laterally wedged insole compared with a neutral insole, and a strapped insole has more adverse effects than a lateral wedge insole[25]. Haim *et al*[27] evaluated whether a biomechanical training program could effectively reduce knee adduction moments at 3 and 9 mo in which his results showed not only was there a significantly reduced knee adduction moment, there were also reduced pain and improved function in these subjects with bilateral knee OA[27]. While studies suggest the potential benefit from knee braces, knee sleeves, foot orthoses, and biomechanical training programs, they also highlight the need for more high quality studies which are currently lacking and for more effective ways to determine which subset of knee OA patients are likely to benefit from these interventions. Future research can include utilization of video gait analysis and 3D motion analysis using computer software to further assess biomechanics and individualize interventions in correcting abnormalities.

PHARMACOLOGICAL TREATMENT

Oral analgesics/anti-inflammatories

Several oral medications are prescribed for treatment of knee OA, mostly addressing the issue of pain. Many supplements are available in the United States that claim to be effective in the treatment of OA, however, few have been well studied for efficacy. Additionally, supplements are not held to the same product quality standards as FDA approved medication and thus variability in product may exist from company to company further making it difficult to determine if certain supplements are beneficial and if they should be considered in the management of knee OA. Glucosamine/chondroitin is the most extensively studied supplement for the treatment of knee OA. This oral supplement is alleged to be absorbed and incorporated into articular cartilage thus potentially allowing for the halting of disease progression and even reparative process[28]. There have been many conflicting studies showing both efficacy and lack of efficacy of glucosamine and/or chondroitin supplements which may be partially due to the difference in quality of products being such as those that are pharmaceutical grade. Fransen *et al*[29] in a double-blind randomized placebo-controlled trial showed that the combination of glucosamine-chondroitin resulted in a statistically significant reduction in joint space narrowing at 2 years of use. While there was also a reduction in knee pain over the study period, none of the groups reach a reduction of pain that statistically significant compared to placebo[29]. In a review of the available literature, many studies demonstrated OA pain relief with glucosamine and chondroitin sulfate use and given its excellent safety profile that is equal to placebo in most studies, this therapy is suggested as one that should be discussed with patients regarding potential benefits and considered as an initial treatment modality[30]. Acetaminophen has been commonly used for the treatment of knee OA and a Cochrane review in 2006 including fifteen RCTs involving 5986 participants showed acetaminophen was superior to placebo in five of the seven RCTs, however, when compared to NSAIDs the evidence suggested that NSAIDs were superior to acetaminophen for the treatment of knee OA[31]. Additionally, acetaminophen had previously been viewed as a safe medication to use as a short-term analgesic of knee OA based on a 2010 systematic review that found a low-level effect for OA pain, however, both this review and a safety review in 2012 have raised concern of its safety profile and suggest that this medication should be used more conservatively in both dosing and duration[32,33]. Many studies have demonstrated the ability for NSAIDs to provide symptoms relief for knee OA with the American Academy of Orthopaedic Surgeon's (AAOS) "Treatment of Osteoarthritis of the Knee: Evidence-Based Guideline, 2nd Edition" concluding that NSAIDs as a group should be recommended for patients with symptomatic OA of the knee and it received a strong strength of recommendation. This was determined after 19 studies were included for review with 202 favorable outcomes comparing either selective, non-selective, or topical analgesics to placebo. Out of the 202 total outcomes, 171 were statistically significant in favor of the experimental group. Fifteen outcomes were above the MCII threshold and 63 outcomes were possibly clinically significant[34]. While NSAIDs should be recognized as a good short-term treatment to manage symptomatic knee OA, it is important to acknowledge their side effect profile which makes this medication class a poor long-term treatment. A comparative effectiveness review in 2011 indicated that NSAIDs are associated with an increased risk of serious gastrointestinal (GI), cardiovascular (CV), and renal injury when compared to placebo[35]. The review also found that Celecoxib had a lower risk of ulcer complications compared to non-selective NSAIDs but had a moderately higher risk of CV complications highlighting the need to use NSAIDs conservatively by limiting dosage to lowest required to achieve pain relief and avoid prolonged use[35]. For those with a moderate comorbidity risk of GI complications,

a proton-pump inhibitor should be considered for co-prescribing with non-selective NSAIDs or this medication class should be avoided all together if there is a high risk. Topical NSAIDs can also be considered as a safer and better tolerated treatment although they have a higher risk of dermatological adverse effects. Tramadol and opioids have been evaluated as medications that may offer pain relief for symptomatic OA. Although opioids were found to have a small to moderate benefit compared to placebo in a 2009 Cochrane review, these benefits were outweighed by large increases in the risk of adverse events and therefore it was recommended they not be routinely used, even if osteoarthritic pain is severe[36]. Tramadol has been studied due to its increasing use for the treatment of OA since it does not produce GI bleeding or renal injury compared to NSAIDs. However, similarly to opioids, its benefits appear to be small in relation to pain reduction with a number of adverse events that cause participants to stop taking the medication[37]. While there are a variety of medications available to help reduce pain related to knee OA, their safety profiles need to be considered when initiating treatment and these should not be viewed as good long term treatment modalities in the management of knee OA.

Disease-modifying osteoarthritis drugs

Disease-modifying osteoarthritis drugs (DMOADs) are drugs that halt or significantly slow the progression of structural joint degeneration, specifically cartilage destruction. Several drugs have been investigated including the tetracycline antibiotic, doxycycline, as *in vitro* studies have shown that it may possess the ability to inhibit collagen degradation. Brandt *et al*[38] conducted a randomized, placebo-controlled, double-blind trial studying subjects with knee OA and measured if joint space narrowing in the medial femorotibial compartment could be reduced with doxycycline. The treatment group received 30 mo of 100 mg of doxycycline twice a day and after 30 mo, the treatment group had 33% less joint space narrowing on radiographic imaging compared to the placebo group. Doxycycline did not reduce the mean severity of joint pain and did not have any effect on either joint space narrowing or pain in the contralateral knee[38]. Additionally, when Snijders *et al*[39] evaluated doxycycline in the management of knee OA in their triple-blinded, randomized controlled trial, it was not effective in reducing symptoms over a 24-wk study period and was associated with an increased risk of adverse events[39]. Bisphosphonates have been studied after they have shown the ability to slow progression of OA in animal models and have decreased pain in states of high bone turnover[40]. When the Knee OA Structural Arthritis study tested the efficacy of risedronate in providing symptom relief and slowing disease progression in patients with knee OA, risedronate did not improve signs or symptoms of OA and did not alter progression of OA compared to placebo, however, it did show a reduction in the level of a marker of cartilage degradation[40]. Strontium ranelate is another drug that has been studied because it has been shown to be able to inhibit subchondral bone resorption and increase cartilage matrix *in vitro*. The SEKOIA trial was a 3-year randomized, double-blind, placebo-controlled trial that studied patients with moderate knee OA who received strontium ranelate 1 g/d, 2 g/d, or placebo. Treatment with strontium ranelate decreased progression of knee OA with estimates for annual difference in joint space narrowing versus placebo found to be 0.14 mm for 1 g/d and 0.10 mm for 2 g/d, with no difference between strontium ranelate groups and all values reaching statistical significance. Strontium ranelate 2 g/d also improved WOMAC total score and pain subscore with the treatment being well tolerated[41]. The SEKOIA trial has sparked more interest in strontium ranelate and has led to further studies that are currently underway which include evaluating its effect on loss of cartilage volume and bone marrow lesions using quantitative MRI. While these drugs will continue to be studied in order to more clearly understand their potential role in the management of knee OA, they will also stimulate new research into other DMOADs in hopes of providing better options to those suffering from the progressive nature of knee OA.

Intra-articular corticosteroid injections

Intra-articular (IA) corticosteroid injections for knee OA appear to be an effective way to decrease pain in the short-term and should be used when signs of inflammation arise. A 2006 Cochrane review of the current literature found that IA corticosteroids were more effective than the placebo group for pain reduction and patient global assessment at 1 wk post-injection. There was continued effect seen between 2 and 3 wk post-injection but at 4-24 wk, there was a lack of evidence of effect on pain and function. Comparing IA corticosteroids to IA hyaluronic acid injections, there was no statistically significant difference between weeks 1-4, however, between 5-13 wk post-injection, IA hyaluronic acid was more effective than IA corticosteroids for one or more of the following variables: WOMAC OA Index, Lequesne Index, pain, range of motion (flexion), and number of responders. The review concluded that IA corticosteroid injections appear to offer good short-term benefits with less evidence to support long term benefit[42]. Another review by Bannuru *et al*[43] compared the efficacy of IA hyaluronic acid with corticosteroids for knee OA. While there short-term analysis differed slightly from the Cochrane review in that the results from baseline to 4 wk showed that IA corticosteroids appear to be relatively more

effective for pain than IA hyaluronic acid, it similarly found that after 4 wk the IA hyaluronic acid continued to show superiority over IA corticosteroids further supporting the notion that IA corticosteroids should be implemented for reducing acute inflammation and relieving pain in the short-term but it is not a good treatment option for long-term management of knee OA[43].

Hyaluronic acid injections

Hyaluronans are also known as sodium hyaluronate or hyaluronic acid. Hyaluronic acid is a natural complex sugar of the glycosaminoglycan family and a normal component of synovial fluid and cartilage in the knee. Its viscosity and elasticity allow it to act as both a joint lubricant and shock absorber, respectively. Hyaluronic acid injections, often referred to as viscosupplementation, are marketed in the United States as several different formulations with some being produced from rooster comb and some from fermentation of the nonpathogenic bacterium Streptococcus zooepidemicus. The different products also vary by molecular weights, concentration of hyaluronic acid, elasticity, viscosity, and number of injections per treatment course[44]. A systematic review in 2011 showed evidence of a small but significant efficacy of IA hyaluronic acid injections for knee OA pain by week 4 post-injection with a moderate clinical significance at week 8 and continued residual benefit until 24 wk[45]. Another review, already mentioned in the previous section, compared IA corticosteroids to hyaluronic acid injections and demonstrated IA hyaluronic acid's superiority over corticosteroids after 4 wk post-injection[43]. The AAOS' "Treatment of Osteoarthritis of the Knee: Evidence-Based Guideline, 2nd Edition" gave a controversial recommendation in 2013 in which it stated they "cannot recommend" using hyaluronic acid for patients with symptomatic knee OA which was a change from their earlier 2008 recommendation that was "inconclusive" based on the available studies to recommend for or against IA hyaluronic acid injections. This update came from changes in their article selection criteria for analysis that included 14 studies, 3 of which were of high strength and 11 of moderate strength. Despite their negative recommendation, their meta-analyses of WOMAC pain, function, and stiffness subscales scores all found statistically significant treatment effects of IA hyaluronic acid compared to placebo and the WOMAC pain and WOMAC total score each were found to be clinically significant but not all of the improvements met the minimum clinically important improvement thresholds (MCII) established by the AAOS panel[34]. It should be noted that their application of the MCII has been called into question by several organizations including the Arthroscopy Association of North America who criticized the statistical analysis and inappropriate use of MCII[46]. A Cochrane review that included 40 trials comparing IA hyaluronic acid to placebo found that at the 5-13 wk post-injection period there was an improvement from baseline of 28%-54% for pain and 9%-32% for function for those receiving IA hyaluronic acid injections for knee OA. They did not find any of the different available hyaluronic acid products to be superior over another and there were very few adverse events reported in the studies. They concluded that viscosupplementation is an effective treatment for OA of the knee with benefits on pain, function, and patient global assessment. The authors also concluded that this review supports the use of the hyaluronic class of products in the treatment of knee OA and that these products provide not only statistically significant effects but also clinically important ones[47]. Some question the true efficacy of IA hyaluronic acid injections because a large placebo effect has been appreciated in several studies being as high as 30%-40%. However, reasons for this large placebo effect may include patient expectation, the Hawthorne effect of participating in a clinical trial, some "placebo" groups were actually receiving an active treatment of saline and/or arthrocentesis, and studies may not account for rescue analgesia or co-therapy being used simultaneously. The safety profile of hyaluronic acid injections is overall minimal. The most common side effects are joint effusion, arthralgia, joint warmth, and injection site erythema which all occur in less than 2.5% of patients and are clinically manageable with short-term use of ice, NSAIDs and do not have long-term sequelae[48-51]. The hylan G-F 20 product appears to have a unique side effect termed a local pseudoseptic reaction in those receiving more than one course of treatment which is hypothesized to be due to the chemical cross-linking used to increase the molecular weight and may occur in up to 21% of patients[52]. This event is not a contraindication to using other hyaluronic acid products and there is no increased risk of recurrence using other products. It should be emphasized that hyaluronic acid injection's excellent safety profile makes it a more appealing treatment for long-term use compared to NSAIDs which have risk of gastrointestinal, renal, and cardiovascular complications. Hyaluronic acid injections also have no known medication interactions making it a good option for patients on multiple medications. Overall, the body of literature appears to support the use of IA hyaluronic acid injections for the treatment of knee OA and future studies of high-quality will continue to be helpful to determine the most appropriate utilization in clinical practice.

Platelet-rich plasma

The use of platelet-rich plasma (PRP) has expanded over the past several years to not only just include the treatment of tendon and ligament injuries, but

also in the treatment of cartilage injuries such as in knee OA. PRP is derived from centrifuging whole blood in order to obtain a platelet concentration above baseline[53]. Growth factors including platelet-derived growth factor (PDGF), insulin growth factor (IGF), vascular endothelial growth factor, and transforming growth factor beta-1 are believed to be key components of PRP for structural repair. Drengk *et al*[54] showed that PRP has a proliferative effect on autologous chondrocytes and mesenchymal stem cells in an *in vitro* study. When Petrera *et al*[55] compared chondrocytes supplemented with either fetal bovine serum, PRP, or platelet-poor plasma, the presence of PRP in the culture media enhanced the *in vitro* formation of cartilage the most with increased glycosaminoglycan content, greater compressive mechanical properties, and maintained characteristics of hyaline phenotype. A randomized control trial involving dogs with documented symptomatic arthritis in a single joint was conducted by Fahie *et al*[56]. Dogs in the test group received a single injection of PRP in the affected joint and the control group dogs received a saline injection in the affected joint. After 12 wk, comfort and function improved by 55% and weight placed on the affected limb improved by 12% in the PRP group compared to the control group[56]. Further helping to understand ways in which PRP may be helpful in treating knee OA regarding anti-inflammatory effects, van Buul *et al*[57] in the Netherlands showed that PRP reduced several different effects of interleukin (IL)-1β which is involved in the catabolic process of articular cartilage in knee OA. Kon *et al*[58] did a prospective study on 115 knees with OA receiving a series of 3 PRP injections in which statistically significant improvement of all clinical scores was observed at 12 mo with maximum improvements at 6 mo[58]. Several studies have compared PRP to hyaluronic acid with each of them demonstrating positive results for these treatments of knee OA compared to placebo. PRP and hyaluronic acid have shown similar results in older patients with more advanced OA but PRP has shown better results compared with hyaluronic acid in younger patients affected by cartilage lesions or early OA[59-61]. When Cerza *et al*[61] compared PRP to hyaluronic acid, PRP was found to be more effective and there was also no statistically significant difference in the effect of PRP with regards to the severity of the knee OA. These findings counteract the argument that PRP is only helpful for milder cases of knee OA. Patel *et al*[62] compared 1 *vs* 2 PRP injections to treat knee OA and they found a single dose of PRP to be as effective as 2 injections to alleviate symptoms in early knee OA which further questions whether multiple subsequent injections are needed rather than a single injection only. A prospective cohort study following patients 1 year after PRP therapy for knee OA was conducted by Halpern *et al*[63]. Twenty-two patients with a Kellgren grade of 0-Ⅱ with knee pain were treated with PRP for early knee OA which was confirmed with a baseline MRI. Pain scores significantly decreased by 56.2% at 6 mo and 58.9% at 12 mo with 88% of patients showing improvement of at least 25% at 12 mo. Additionally, WOMAC overall score improved by 45.1% at 6 mo and 56.2% at 12 mo. In this same study by Halpern *et al*[63], qualitative MRIs demonstrated no change in the medial knee compartment in 73.3% of cases at 1 year despite the expected typical progression of knee OA and joint space narrowing. A systematic review of 59 articles (26 *in vitro*, 9 *in vivo*, 2 both *in vivo* and *in vitro*, and 22 clinical studies) analyzing the use of PRP for joint degeneration reinforced that the preclinical literature shows an overall support toward PRP with clinical studies displaying positive effects of PRP with a more significant benefit appearing to be in the younger patients with earlier stages of knee OA[64]. Cavallo *et al*[65] demonstrated that a comparison of different PRP formulations induced distinct effects on human articular chondrocytes *in vitro*, likely attributable to the differences in the concentrations of platelets, leukocytes, growth factors, and other bioactive molecules. This study highlights the fact that differences in technique and PRP composition may produce different outcomes when treating knee OA and make it difficult to compare results between various studies. However, it does appear that PRP can be a useful treatment for knee OA and certainly additional studies are needed before conclusions regarding true efficacy can be confirmed. Future studies are also needed to determine the optimal composition of PRP (*i.e.*, platelet concentration, leukocyte-rich or poor).

Stem cells

Mesenchymal stromal cells [mesenchymal stem cells (MSCs)] are multipotent cells that can be isolated from several human tissues. The immunomodulatory, reparative, and anti-inflammatory properties of MSCs have been tested in a variety of animal models and appear to have potential clinical applications which includes tissue repair[66]. One such study used scaffold-free MSCs obtained from bone marrow to directly inject intra-articularly in a rabbit model of OA. OA was induced by transecting the anterior cruciate ligament of the knee joint of rabbits and radiological assessment confirmed the development of OA after 12 wk. The rabbits then received either MSCs or medium without MSCs and at 20 wk post-operatively, the rabbits receiving the MSCs showed a lower degree of cartilage degeneration, osteophyte formation, and subchondral sclerosis compared to the control group[67]. While the exact mechanism by which MSCs are able to regenerate articular cartilage in patients with OA is not exactly clear,

these cells can induce proliferation and differentiation of resident progenitor cells and they have an innate differentiation potential to chondrocytes[68]. Orozco *et al*[69] conducted a pilot study where 12 patients with chronic knee pain unresponsive to conservative treatments and radiologic evidence of OA were treated with autologous expanded bone marrow MSCs by IA injection. They found that the patients exhibited rapid and progressive improvement in function that approached 65% to 78% by 1 year and that quantification of cartilage quality by T2 relaxation measurements demonstrated a highly significant decrease of poor cartilage areas (on average, 27%), with improvement of cartilage quality in 11 of the 12 patients[69]. This study, however, contained a small patient number and there was no control group for comparison. When Filardo *et al*[70] conducted a systematic review of the use of MSCs for the treatment of cartilage lesions, they included 72 preclinical papers and 18 clinical trials. In regards to the clinical trials focusing on cartilage degeneration, there were no randomized trials, 5 comparative studies, 6 case series, and 7 case reports. Of further note, 2 involved the use of adipose-derived MSCs, 5 the use of bone marrow concentrate, and 11 the use of bone marrow-derived MSCs. While multiple studies showed positive effects of MSCs for the treatment of OA or other cartilage defects, the authors acknowledge that these results are preliminary data on this topic due to only having available preclinical studies along with clinical studies that are of low quality due to weak methodology, small number of patients, and short-term follow-up[70]. Safety concerns have also arisen surrounding the use of MSCs which include but not limited to the neoplastic potential of MSCs due to their proliferative capacity and susceptibility to infection given their immunomodulatory effects[71]. In a systematic review by Lalu *et al*[71] to evaluate the safety of MSCs, they did not identify any significant safety issues other than a transient fever and concluded that this review should provide some assurance that MSC therapy appears to be safe. As in PRP, the use of MSCs is a therapy in that it goes beyond simply attempting to treat symptoms and instead offers the potential to stop disease progression and regenerate articular cartilage. While the possibility of such a regenerative treatment for knee OA is intriguing, before this therapy can be recommended confidently for clinical use there needs to be further studies that are of higher quality to better determine the efficacy, safety, and optimal source and preparation of cells for the treatment of knee OA.

Other injectables

Several other emerging injection therapies have been evaluated although the amount of quality studies are lacking or are still in early trial phases making it difficult to provide appropriate judgment on the efficacy of these products for the treatment of knee OA. IA botulinum toxin type A (BoNT-A) is hypothesized to have anti-nociceptive and potentially anti-inflammatory effects. Boon *et al*[72] conducted a pilot study to evaluate IA BoNT-A in painful knee osteoarthritis. Subjects were randomized to receive a single injection of corticosteroid, low-dose BoNT-A (100 units), or high-dose BoNT-A (200 units). The primary end point was pain visual analog scale score at 8 wk, which decreased in each group but only the low-dose BoNT-A group achieved statistical significance. Each of the groups did show statistically significant improvements in WOMAC Index scores (pain, stiffness, function) at 8 wk and there were no serious adverse events were noted in any group. The study overall supported a possible role for BoNT-A as a treatment option for symptomatic knee OA however it was recognized that larger double-blind randomized studies are needed[72]. Bone Morphogenic Protein-7 (BMP-7) has been studied due to its apparent strong anabolic effect on cartilage as it stimulates synthesis of cartilage matrix components, increases proteoglycan and collagen synthesis, while antagonizing catabolic mediators of cartilage such as IL-1[73]. In a rabbit model, Badlani *et al*[73] delivered BMP-7 *via* an osmotic pump to the knee 4 wk after ACL transection and when compared to a control group for the progression of knee OA, the BMP-7 group showed less cartilage degradation than the controls. In a phase I safety and tolerability study of BMP-7 for symptomatic knee OA, results showed that by week 12, all treatment groups with BMP-7 and the placebo group had improvement in pain scores with a trend toward more symptomatic improvement in the BMP-7 treatment groups although statistical significance was not achieved[74]. Fibroblast growth factor-18 (FGF-18) has also been studied for use as an IA injection to treat knee OA. Moore *et al*[75] demonstrated in animal models that there FGF-18 increased chondrogenesis and cartilage repair. Lohmander *et al*[76] conducted a proof-of-concept double-blind placebo-controlled randomized trial to evaluate the efficacy and safety of IA sprifermin, a recombinant human FGF-18, in patients with symptomatic knee OA. Their results found no statistically significant dose-response change in central medial femorotibial compartment cartilage thickness. Sprifermin though was associated with statistically significant dose-dependent reductions in loss of total and lateral femorotibial cartilage thickness and volume and in joint space width narrowing in the lateral femorotibial compartment with no association with any local or systemic safety concerns[76]. Other IA injection being studied for treatment of knee OA include IL-1 inhibitor, PDGF, IGF, amongst several others currently being studied. While trial data and preliminary studies have been

done for many of these therapies, more studies are needed to establish that they are both effective and safe.

OPERATIVE MANAGEMENT

This review has discussed many non-operative treatments that are utilized to prolong the need for total knee arthroplasty (TKA), however, there are other surgical procedures that are sometimes performed as alternatives in hopes of preventing the need for TKA. These surgical procedures include arthroscopy, high tibial osteotomy to correct abnormal alignment, and unicompartmental knee arthroplasty. High tibial osteotomy and unicompartmental knee arthroplasty are potential alternatives if only a single compartment is involved with more data supporting unicompartmental knee arthroplasty as a good treatment option in this scenario. An in depth discussion of these surgical procedures are beyond the scope of this review article, although it is important to note that arthroscopy, in the vast majority of patients, is no longer viewed as an appropriate treatment for knee OA or for meniscal degeneration in the setting of significant knee OA. Moseley *et al*[77] conducted a randomized, placebo-controlled trial in which a total of 180 patients with knee OA were randomly assigned to receive arthroscopic debridement, arthroscopic lavage, or placebo surgery consisting of skin incisions with a simulated debridement without insertion of the arthroscope. Outcomes were assessed at multiple points over a 24-mo period and they were no better after arthroscopic lavage or arthroscopic debridement than after a placebo procedure[77]. Another randomized, controlled trial was conducted by Kirkley *et al*[78] comparing surgical lavage and arthroscopic debridement together with optimized physical and medical therapy to treatment with physical and medical therapy alone. Arthroscopic surgery for knee OA was shown to provide no additional benefit to optimized physical and medical therapy and even analyses of WOMAC scores at interim visits and other secondary outcomes also failed to show superiority of surgery[78]. Arthroscopy has also been commonly used in the setting of knee OA to treat meniscal tears, although it is critical to recognize that in a study of incidental findings on knee MRI, among persons with radiographic evidence of knee OA, the prevalence of a meniscal tear was 63% in those who had knee symptoms and still remained 60% among those without symptoms[79]. When comparing surgical intervention to conservative management for meniscal degeneration in the setting of knee OA, outcomes are no better for those undergoing surgical intervention[80,81]. Based on the current literature comprised of several high-level studies, arthroscopy should not be included in the treatment algorithm for knee OA, especially without evidence of mechanical symptoms such as knee locking, as it is has not been shown to be an effective method to treat changes seen in the setting of knee OA which include degeneration of the articular cartilage and menisci.

CONCLUSION

The management of knee OA is of growing importance in the world and especially in the United States where an aging population and increasing trends in obesity are increasing the prevalence of this disease. Not only is this disease a burden on the individual patient, it is a burden on the healthcare system and overall economy. Treatment has traditionally focused on symptom control with some attention being given to prevention strategies and only more recently has there been a greater emphasis placed on trying to develop new modalities that aim to slow disease progression or even reverse the process. While there are many treatments available for knee OA, this review has attempted to provide evidence from the available literature to help guide management with the understanding that some of these modalities may be better options depending on the individual patients and clinical scenario. It is important to recognize the complex pathophysiology of this disease process and that a multi-faceted treatment approach is necessary to improve pain and function. Based on this review, education and self-management strategies should always be a part of managing knee OA as it can be used in conjunction with other treatments. Weight loss should be encouraged for patients who are overweight along with an beginning an exercise program that may involve a combination of aerobic activity, strengthening, and improving flexibility. While the optimal program regimen may be debatable, the literature demonstrates that they offer benefit to patients with knee OA and that weight loss with exercise is better than either one alone. There are several studies that have looked at the usefulness of biomechanical interventions and many of them have demonstrated potential benefit from knee braces, knee sleeves, foot orthoses, and biomechanical training programs warranting their incorporation into the management of knee OA. However, more studies are needed to better determine which patients specifically will benefit most from these various interventions. Glucosamine/chondroitin is a supplement with conflicting studies which may be partially due to the difference in quality of products being used in the studies, however, with its excellent safety profile and some studies demonstrating its superiority to placebo, it is a therapy that should be discussed with patients for potential use. Acetaminophen and NSAIDs, and to a lesser extent Tramadol and opioids, can be helpful in the short-term management of knee OA, but given their side effect profiles, they should be considered a poor long-term treatment. DMOADs were discussed in this review to

present available literature on oral medications being studied to alter the course of knee OA, however, at this time there is not enough evidence to suggest the common use of these treatments in managing knee OA. Injectables are another category of treatment for knee OA that should be considered beginning with the use of IA corticosteroids that have shown the ability to decrease pain in the short-term and should be used when signs of inflammation arise. The body of literature overall supports the use of IA hyaluronic acid injections for the treatment of knee OA and demonstrates it is a superior option for long-term management of knee OA compared to IA corticosteroids. Additionally, hyaluronic acid has an excellent safety profile making it a more suitable for being used for an extended period of time.

PRP is another injectable that when compared to hyaluronic acid has shown similar results in older patients with more advanced OA and may have better results in younger patients affected by cartilage lesions or early OA. PRP should be considered as a treatment option especially if the patient has used the other injectables mentioned without success, however, additional studies are needed before conclusions regarding true efficacy can be confirmed and these studies are also needed to help determine the optimal composition of PRP (*i.e.,* platelet concentration, leukocyte-rich or poor). The use of stem cells is emerging and while the possibility of such a regenerative treatment for knee OA is intriguing, before this therapy can be recommended confidently for clinical use there needs to be further studies that are of higher quality to better determine the efficacy, safety, and optimal source and preparation of cells for the treatment of knee OA. Several other emerging injection therapies were discussed in this review, but the amount of quality studies are lacking or are still in early trial phases making it difficult to provide appropriate judgment on the efficacy and safety profile of these products for the treatment of knee OA. While surgical interventions for knee OA were beyond the scope of this review, the current literature comprised of several high-level studies provide evidence that arthroscopy should not be included in the treatment algorithm for knee OA as it has not been shown to be an effective method to treat changes seen in the setting of knee OA with degeneration of the articular cartilage and menisci. This review hopes to provide a better understanding of treatment options available and their efficacy but it is important to highlight the need for continued research with regards to the management of knee OA. This research should focus on investigating the efficacy of new drugs such as the DMOADs or injectables as well as better understanding their safety profiles. Rather than develop treatments that target symptoms, the emphasis needs to be on developing advanced therapies that can slow or prevent further disease progression and hopefully even initiate a regenerative process. Additional research should also be directed at determining which subset of patients with knee OA may benefit from certain treatments and who are more likely to have a positive response to a given intervention so that more individualized treatment strategies can be established.

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