ORTHOPEDICS AND SPORTS MEDICINE

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Guest Editor

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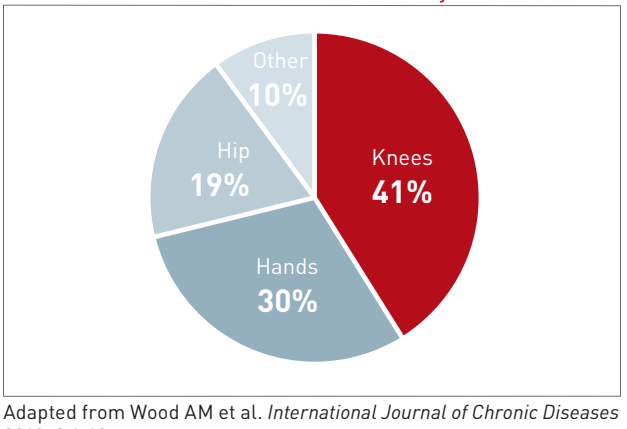
Osteoarthritis of the Knee: Addressing a Growing Epidemic

Osteoarthritis (OA) of the knee is a common orthopedic complaint, affecting about one in six adult Canadians.[1] A chronic and progressive inflammatory condition, OA is painful, restricts activity, and impairs quality of life. Due to its chronicity, it is essential to consider the long-term safety and tolerability of therapeutic options in the context of extended symptom control. Strategies to slow the pace of joint deterioration are being pursued, but the current focus of intervention is on symptom control. Traditionally, such simple analgesics as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) have been the first-line option, but their efficacy is limited and there are safety concerns with chronic use. For localized joint injections, hyaluronic acid (HA), which is a component of normal joint physiology, has safety advantages over corticosteroids, particularly when repeated treatments are anticipated. The durability of the effect of HA is also an advantage relative to other options. The success of any therapy is likely to be increased with non-pharmacologic support, particularly exercise to strengthen joints.

Background

Osteoarthritis (OA) involves deterioration of the cartilage and interdependent joint tissues, including the bone.[2] Attributed to repeated stress on joint tissues, OA can occur in any joint but is particularly common in joints of the limbs, such as the knee, hip, hands (Figure 1).[3] The risk factors for knee OA, reinforcing the role of stress, include exceptional bending such as required in some occupations, obesity, and knee surgery or other trauma.[4] The prevalence of OA climbs with age but is not confined to the elderly. According to U.S. data, the overall prevalence of OA in adults is 13.9% but reaches 33.6% in those aged 65 years or older.[5] The lifetime risk of OA, which is a leading cause of disability,[6] is 44.7%, rising to 56.8% in those with a history of knee injury.[7]

FIGURE 1 | OA Found Most Commonly in the Knee



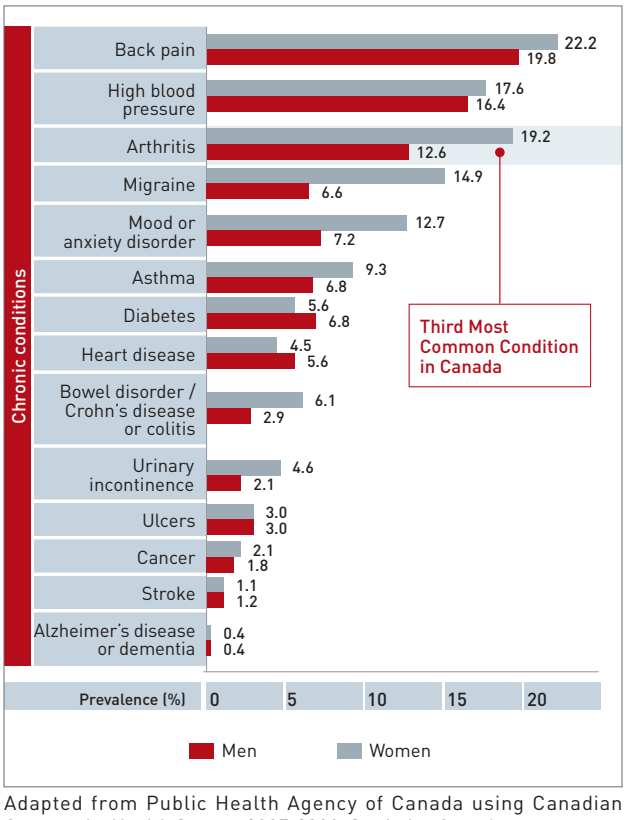
Adapted from Wood AM et al. *International Journal of Chronic Diseases* 2013; 2:1-10.

In Canada, arthritis of all types collectively represents the third most common chronic condition with a peak prevalence in late middle age (Figure 2).[8] Of the arthritis types and joints affected, knee OA represents a large and increasing public health burden due to rising rates of obesity and an aging population.[9] The estimated costs are substantial, stemming not only from healthcare services for OA, which is the most frequent indication for knee replacement,[10] but restrictions imposed by the disease on normal function, including occupational activities.[11,12] Evidence that symptomatic knee OA has been increasing at rates not fully explained by rising rates of obesity emphasizes the need for structured use of rational management strategies.[13]

Knee OA Pathology and Risk of Progression

In patients with knee OA, structural joint deterioration is the common characteristic within a broad range of clinical and radiological presentations. Focal areas of abnormality may affect a range of tissues other than hyaline articular cartilage, including ligaments and bone.[14] When cartilage loss is sufficient, bony remodeling may occur, producing malalignment.[15] This malalignment can trigger further cartilage loss and damage that underlies progression (Figure 3). The risk and speed of progression is variable. In some individuals, symptoms remain relatively stable

FIGURE 2 | Self-reported Prevalence of Specific Chronic Conditions by Sex: Canada, 2007-2008



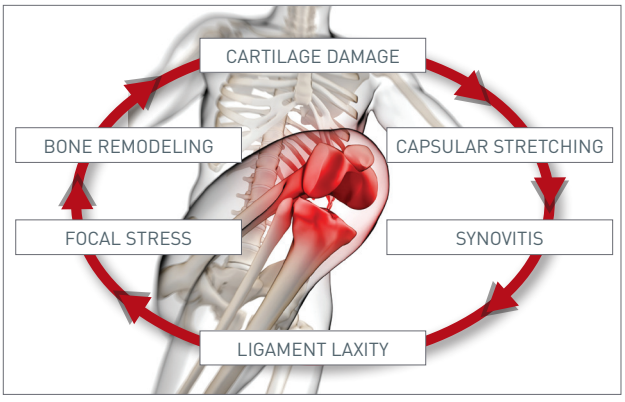
Adapted from Public Health Agency of Canada using Canadian Community Health Survey, 2007-2008, Statistics Canada.

for extended periods. In others, synovitis and other forms of inflammation exacerbate joint deterioration, leading eventually to disability best relieved with joint replacement.[16]

Radiological findings vary markedly and may not uniformly correlate with symptoms.[17] Several radiographic grading systems for assessing the severity of knee OA have been proposed. Of these, the Kellgren and Lawrence classifications, which were described more than 40 years ago,[18] are typical and remain widely used. In this system, the four classifications after grade 0 (no abnormality) range from modest osteophytic lipping (grade 1) to deformity of the bone contour (grade 4) (Table 1).

The cardinal signs of knee OA, according to guidelines from the American College of Radiology (ACR) and others, include pain, transient morning stiffness, and crepitus on motion.[19] The accuracy of a physical examination for making the diagnosis of knee OA increases with other classic features, such as bony tenderness and malalignment,[20] but imaging will be useful in the substantial minority of patients with an atypical presentation.[21] Although radiographs may be normal in patients with early OA,[22] other types of imaging studies, such as MRI and ultrasound, can provide additional information when used alone or in combination.[23] Laboratory tests are not useful for the diagnosis of OA but they may be of value for ruling out alternative diagnoses, such as gout or infection.

FIGURE 3 | Vicious Cycle of Knee OA



Adapted from Felson DT. *N Engl J Med* 2006;354:841-8.

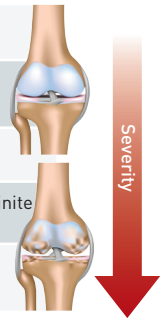
Managing OA: Goals of Therapy

The goal of treatment is to alleviate symptoms and prevent progression. A combination of pharmacological and non-pharmacological treatments is typically appropriate. There is no cure for knee OA, but treatments to improve quality of life and slow or halt progression of joint deterioration can be expected to yield both immediate and long-term benefits.

Among oral therapies for symptom control, non-steroidal anti-inflammatory drugs (NSAIDs) are modestly more effective than acetaminophen,[24] but the toxicity of NSAIDs, including COX-2 inhibitors, is cumulative.[25,26] Strategies to reduce the gastrointestinal effects of non-selective NSAIDs by agents that suppress gastric acid have been effective,[27] but long-term use of both COX-2 inhibitors and NSAIDs pose risks, particularly nephrotoxicity.[28,29] Glucosamine and chondroitin are safer but appear to be even less effective than simple analgesics. Although several relatively small controlled trials have associated these agents with benefit,[30,31] a multicenter trial with four arms was unable to show a statistical advantage for either glucosamine or chondroitin relative to placebo after 24 weeks of therapy.[32]

TABLE 1 | Kellgren & Lawrence Classification System of Knee Osteoarthritis Severity

Grade 0	No radiographic evidence of OA
Grade 1	No joint space narrowing (JSN) but possible osteophytic lipping
Grade 2	Definite JSN and definite osteophytes
Grade 3	Moderate and multiple osteophytes, definite JSN, sclerosis, possible bony deformity
Grade 4	Large osteophytes, marked JSN, severe sclerosis and definite bony deformity



Adapted from Kellgren JH, Lawrence JS. *Ann Rheum Dis* 1957;16: 494-502.

Of intra-articular injections, there is evidence of benefit from both corticosteroids and from hyaluronic acid (HA). For corticosteroids, pain relief is relatively rapid and attributed to the anti-inflammatory effect, but there appears to be diminishing benefit over time.[33] In a meta-analysis the long-term safety of corticosteroids were found acceptable,[34] but prolonged use does raise theoretical concerns from such issues as change in immune function.[35] Several guidelines, including those from the American Academy of Orthopedic Surgeons (AAOS), do not currently recommend intra-articular corticosteroids for routine care of knee OA.[36]

Intra-articular injection of HA, which is an endogenous glycosaminoglycan found in several tissues of the body, received regulatory approval for the treatment of knee OA almost 20 years ago and is widely used due to a favorable benefit-to-risk ratio. In the knee, endogenous HA is associated with providing viscoelasticity to the synovial fluid, improving distribution of stress.[37] Experimental studies suggest HA may play an active role in chondrocyte repair and knee stability.[38] Clinical studies support longer-term benefit from HA relative to intra-articular corticosteroids and pain relief comparable to NSAIDs.[39] While some patients experience pain on injection, the safety profile of HA is otherwise comparable to placebo.[40]

HA preparations may not be interchangeable. Since the first commercial preparations were made available, subsequent products have been developed for improved safety, efficacy, or both. For example, all initial products were formulated from rooster combs. The avian origin generated labeling that advised caution in individuals allergic to poultry or poultry products. While many newer products are non-avian based, they have the additional advantage of extended activity. The newest non-avian HA products, such as Monovisc and Durolane, are associated with efficacy for up to six months. While this is an advantage for patients with a low tolerance for injections, the longer intervals suggest greater potency of effect that may also be relevant to speed of onset. Relative to initial formulations, many of the recent HA preparations have high molecular weights, which may offer greater potency for tissue repair.[41] Lastly, HA dose formulations vary (Table 2).

Of other pharmacologic options for the treatment of knee OA, most, such as opiates, are used for short-term symptom control. While the theoretical value of HA in restoring normal physiology to halt progression is intriguing, there is no evidence that any drug therapy reverses knee OA progression.

For patients presenting with symptomatic OA, pharmacologic therapy is first-line therapy for symptom control, but non-pharmacological therapy may play an essential role in slowing or preventing disease progression. In patients with knee OA associated with obesity, for example, weight loss is strongly recommended in the AAOS guidelines.[36]

The risks of excess body fat not only include mechanical load but upregulation of pro-inflammatory factors that may contribute to joint pathology.[42] Obesity has also been associated with increased pain perception independent of joint weight bearing.[43] Loss of weight in obese individuals with knee OA has been associated with both symptom relief and slower disease progression.[44]

TABLE 2 | Evolution of Hyaluronic Acid Formulations: Examples

PRODUCT DEVELOPED	PRODUCT EXAMPLES	DOSING Total Tx Dose (mg)
FIRST GENERATION: Multiple Injections	Hyalgan Synvisc*	60/100 48
SECOND GENERATION: Single Dose Injection, Rooster-Comb Derived	Synvisc-One* Gel-One	48 30
RECENT MODIFICATIONS: Single Dose Injection, Non-Avian Formulation, High dose	Durolane Monovisc	60 80

See package inserts.
*Synvisc and Synvisc-One are the same formulation with the latter being supplied in a single syringe instead of three.

Strengthening muscles, particularly quadriceps, is also an effective non-pharmacologic approach to improved joint function.[45] In controlled trials, aerobic and resistance exercises as well as strength training have all been found effective for reducing symptoms of OA with the potential to slow progression.[46,47] As malalignment is considered an important predictor of progression, braces, orthotics, and compression sleeves all have potential benefit in selected patients. In a study of patients with varus malalignment, knee pain was reduced relative to no therapy with a neoprene sleeve.[48] In another study, also recruiting patients with varus malalignment, pain relief was achieved with a lateral wedge orthotic.[49]

Although potentially useful for specific indications, surgical treatments for knee OA have been largely disappointing. In a meta-analysis, joint lavage was not associated with either improved joint function or reduced pain.[50] A similar conclusion was drawn from a meta-analysis of studies of arthroscopic debridement.[51] In a review of other types of surgeries for knee OA, such as osteotomy or joint fusion, none were considered to be appropriate for routine use in European consensus guidelines.[52] Surgical procedures performed for specific goals, such as arthroscopic removal of loose bodies may be appropriate in selected patients, but the value of surgery other than total joint replacement has not been well documented.

A better understanding of the pathophysiology of knee OA is urgently needed to improve therapeutic options. While many of the etiologies of OA are well described, including mechanical joint stress and genetic susceptibility,[53] the specific molecular events that sustain cartilage deterioration remain poorly understood. Targeted therapies in OA as in other diseases may provide the greatest opportunity for tissue repair or regeneration. Autologous chondrocyte implantation is among several techniques with promise to produce durable cartilage repair.[54] Efforts to increase the biologic activity of exogenously administered HA, which has been shown to regulate chondrocyte behavior in experimental studies,[55] is another. Such treatments could play a critical role in lessening the growing burden of knee OA.

Conclusion

Knee OA increases in prevalence with age but is a common source of functional impairments and diminished quality of life even in relatively young and otherwise healthy patients. Early initiation of therapy has the potential to attenuate disease progression when pharmacologic and non-pharmacologic management is combined to control symptoms and modify factors likely to exacerbate joint deterioration. Due to the chronicity of knee OA, the most attractive pharmacologic options are those that pose the lowest cumulative risk of toxicity. NSAIDs and HA have both demonstrated efficacy in knee OA but offer unequal risks of adverse events. The potential for HA to improve joint function over time remains a theoretical reason to consider long-acting and high-dose formulations of agents in this drug class. The search for additional agents with an ability to attenuate the disease process is underway.

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Guest Editor

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Hyaluronic Acid in the Knee: History, Characteristics and Efficacy

In the knee, hyaluronic acid (HA), a naturally-occurring compound with viscoelastic properties, is credited with several physiologic functions associated with joint homeostasis. This includes a role in compression force distribution, tissue lubrication, and regulation of cellular activities.[1] In patients with osteoarthritis (OA) of the knee, a chronic degenerative process that adversely affects both cartilage and bone,[2] viscosupplementation with exogenously-produced formulations of HA has been available for more than 15 years. Direct comparisons between current products remain limited, but the distinctions between treatments are potentially important for clinical activity. These distinctions, which may influence onset and duration of pain relief as well as safety, include composition, molecular weight, and molecular activity. Consideration of the physiochemical properties of HA may also be relevant to the more challenging goal of slowing or preventing further joint deterioration.

Background

Hyaluronic acid (HA), also referred to as hyaluronan or hyaluronate, is a naturally-occurring viscoelastic glycosaminoglycan polysaccharide with polymeric and polyelectrolyte properties.[3] It is found in a variety of human and animal connective tissues besides joint synovial fluid, such as vitreous body, nasal cartilage, and the skin, where it has been injected for cosmetic purposes.[4] Interest in HA as a treatment for osteoarthritis (OA) dates to the early 1970s when human studies were initiated after evidence of benefit in animals (Figure 1).[5] Commercial injectable HA products, which are licensed as a medical device, first received regulatory approval in the late 1990s. The initial and subsequent products, which may not be interchangeable as a result of divergent characteristics, have been evaluated in numerous meta-analyses and data reviews.[6,7]

In patients with OA, as well as many other inflammatory joint diseases, the concentration of endogenous HA is reduced, a change consistent with a concomitant reduction in the viscoelastic properties of the synovial fluid.[8] This change may not be just mechanical. A series of human and experimental studies support a role of HA in numerous biological processes, including matrix remodeling and inhibition of damage from activated cytokines.[9] Its role in signal transduction through interaction with the CD44 receptor on the chondrocyte is implicated in cell proliferation, angiogenesis, and cell migration.[10,11] HA may also be involved in mediating pain perception.[12] Various formulations of HA and biological scaffolds dependent on HA have been developed in a variety of tissue engineering studies, including those for bone, ligament, cartilage, and osteochondral defects.[13-15]

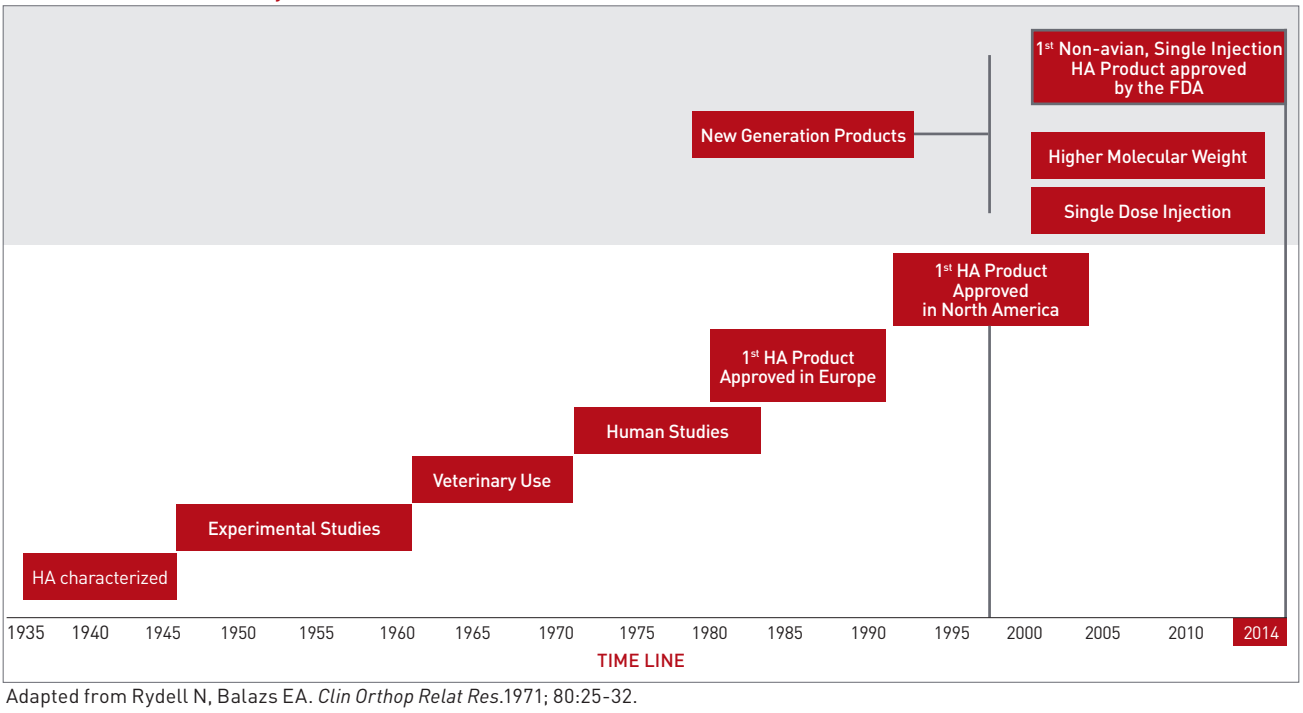
In knee OA, as in the other applications, the composition of exogenous HA may be relevant to its clinical activity. The ideal characteristics of HA in the OA knee are unknown and may vary for objectives such as modification of pain, the inflammatory response, or viscoelastic mechanical properties. Theoretical advantages have driven the development of products that vary for source of HA extraction, molecular weight, cross-linking and other characteristics with potential relevance to half-life in the joint, dosing, duration of pain relief, safety, and preservation of joint integrity.

HA Development: Differing Properties

The first and many early HA products were extracted from rooster combs, which distinguishes them from the non-avian products later derived from bacterial fermentation. The extraction source is a potential safety issue, leading to labeling for avian products that has established a relative contraindication for patients with known allergies to avian products, including poultry, eggs, or feathers.[16] The relatively low molecular weights of earlier HA formulations also predict lower viscosity,[17] a likely disadvantage for stress distribution. The low relative dose concentrations of early products explain the need for more frequent injections to achieve stable pain control.

Recent HA products, which are less often extracted from avian sources, are being engineered to provide durable activity. Several products now demonstrate pain relief sustained for up to 6 months on a single injection. While this prolonged activity may be related to residence time, there is evidence to suggest that modern formulations may also initiate molecular changes, including favorable effects on chondrocyte and synoviocyte behavior, to sustain clinical benefit. To date, there is no compelling evidence to differentiate

FIGURE 1 | Timeline: Hyaluronic Acid as a Treatment for Osteoarthritis

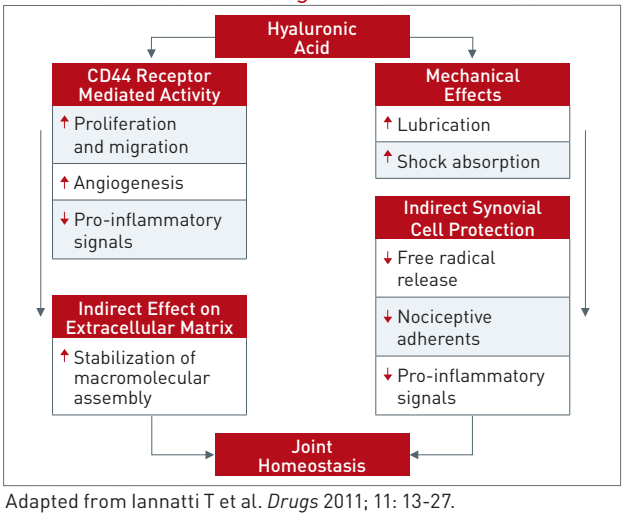


Adapted from Rydell N, Balazs EA. *Clin Orthop Relat Res*.1971; 80:25-32.

HA therapies for disease-modifying effects, but the differences between HA formulations provide a basis for pursuing how properties may alter the underlying disease pathology.

One area of interest is the interaction of HA with the CD44 receptor on chondrocytes as a potentially fundamental step to joint integrity. The CD44 receptor interacts with COX-2,[18] prostaglandins,[18] and osteoblast-mediated osteoclastogenesis,[19] which are all implicated in the homeostasis of joint function. Based on the likelihood that such characteristics as molecular weight affect the ability of HA to interact with CD44, it is reasonable to expect differences in the relative ability of HA formulations to mediate inflammation, extracellular matrix formation, and synovial fluid function (Figure 2).

FIGURE 2 | Maintenance of Joint Homeostasis: Interaction of Hyaluronic Acid with Various Biologic Processes



Adapted from Iannatti T et al. *Drugs* 2011; 11: 13-27.

Evolution of HA Formulations

The putative goal of HA injections is to restore the viscoelastic properties of synovial fluid which is depleted both in the concentration and the molecular weight of endogenous HA.[10] This is based on the premise that improving the mechanical properties of synovial fluid is the mechanism by which HA relieves symptoms. This may be true, but it has not been proven. Alternatively, there is also interest in developing an exogenous HA capable of recreating the full range of biological activities attributed to naturally occurring HA. This includes a homeostatic role that may involve mediation of events that underlie progressive OA.

In the presence of OA, the normal balance between synthesis of new matrix and degradation of aging cartilage is disrupted.[20] The exact cascade of events leading to this disruption is the focus of intensive investigation, but the loss of HA may exacerbate or even drive the process. HA can be linked to the activity of many, if not all, of the factors suspected of participating in OA, including at least indirect exacerbation of loss of aggrecan, a prostaglandin that participates in the integrity of cartilage and which is degraded early in the course of OA.[21]

The potential for HA to exert a protective effect on the cartilage, independent of its ability to restore the viscoelasticity of the synovial fluid, is derived from its ability to bind to the CD44 chondrocyte receptor. While adhesion to the CD44 receptor is associated with chondrocyte proliferation and retention,[22] it is also involved in retaining and anchoring the prostaglandin aggregates important to matrix formation.[23] In experimental studies, HA administration has stimulated production of extracellular matrix proteins such as chondroitin and been associated with increased prostaglandin production.[24,25] Whether a downstream or independent effect, experimental studies have also associated HA with suppression of pro-inflammatory cytokine expression, another factor implicated in progressive OA.[26]

The list of other effects potentially relevant to the homeostatic activity of HA in the knee and the ability of exogenous administration to restore this activity is long and includes protection of chondrocytes against oxidative stress and inhibition of vascular endothelial growth factor (VEGF) and other proteins thought to participate in OA.[27,28] In one set of experiments, cross-talk was demonstrated between HA and inhibitors of COX-2, resulting in a reduction in chondrocyte apoptosis and extending evidence that HA is involved in fundamental molecular pathways mediating joint physiology.[18]

In recreating the effects of endogenous HA for joint homeostasis, there is evidence that molecular weight is a significant variable. In a study of cultured synovial fibroblasts, HA with higher molecular weights produced greater stimulation than HA with lower molecular weights.[29] The authors of this study suggested that exogenous HA of optimal molecular weight may not only exert a greater protective effect but encourage endogenous HA production. In another set of experiments with HA of graded molecular weights, degradation of cartilage and return to a more favorable histology were both improved with higher relative to lower molecular weights.[30,31]

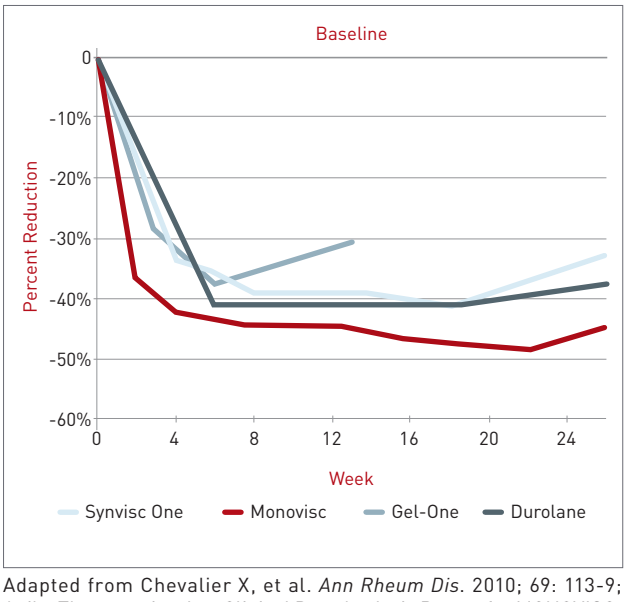
In addition to molecular weight, dose concentration may be one of the most important differentiating characteristics between HA formulations. While a greater volume of active drug per injection has the potential to accelerate the time to drug activity and increase the dwell time, a higher drug concentration may define the ability of one formulation relative to another to both recreate the activities of endogenous HA, but also to stimulate endogenous HA production. In addition to speed and duration of symptom control, these variables may hold the key for developing OA therapies that restore homeostasis and inhibit disease progression.

Clinical Data: Differentiating HA Formulations

There are no large trials to provide objective evidence for a clinically-significant difference between the seven HA products now available in Canada. Recent preference of products that achieve pain control after a single injection is likely to be driven largely by convenience, but newer products based on evolving evidence of favorable HA characteristics, such as relatively high molecular weight, also have theoretical clinical advantages. Trials leading to regulatory approval of these agents have not typically had active comparators, but most of the current devices have labeling that describe an indication for pain relief in patients with OA who have failed to respond to non-pharmacologic therapies or simple analgesics like acetaminophen.

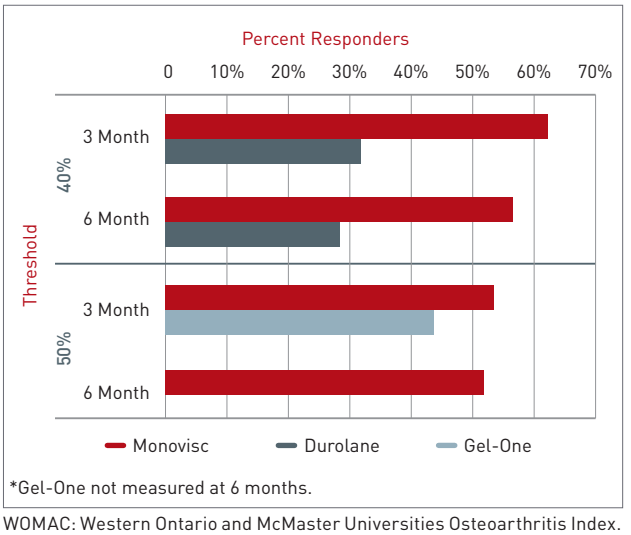
The five single-injection products are Monovisc, Synvisc-One, Gel-One, Neovisc, and Durolane. Multi-injection HA products, like Orthovisc and Synvisc, remain available, but treatments that can be administered with fewer injections are likely to be preferred by patients. Of the single-injection products, Synvisc-One is chemically related to the earlier generation, multidose Synvisc, which is an avian-based product. Gel-One is also avian-based. Monovisc, Durolane, and Neovisc are all non-avian based. Each of these is a member of the most recent generation of HA injection products and has a high molecular weight relative to initial HA formulations. Each has been evaluated in a pivotal, saline-controlled trial with symptomatic relief evaluated out to 26 weeks. From the U.S. Food and Drug Administration (FDA), the current labeling for Monovisc is for the treatment of pain in patients with moderate OA of the knee. Similar labeling has been granted to Synvisc-One, Durolane, and Neovisc. Graphically, non-comparative data indicate that Monovisc may act more rapidly than many of the other current single injection HA formulations (Figures 3 and 4). These data are hypothesis generating in the absence of a randomized trial, but differences in formulation provide an expectation of an unequal onset of action or duration of effect. Relative to other single-injection HAs, the dose concentrations are 80 mg for Monovisc, 48 mg for Synvisc-One, 48 mg for Gel-One, and 60 mg for Durolane (Table 1).

FIGURE 3 | Reduction in WOMAC Pain for Four Single-Injection Hyaluronic Acid Products Over 26 Weeks



Adapted from Chevalier X, et al. *Ann Rheum Dis*. 2010; 69: 113-9; Anika Therapeutics, Inc. Clinical Data Analysis Report for MONOVISC. M. Frank-Molnia, Mar 2012. Data on File; Gel-One Summary of Safety and Effectiveness (Mar 21 2011). P080020. http://www.accessdata.fda.gov/cdrh_docs/pdf8/P080020b.pdf; Altman RD, Akermark C, Beaulieu AD, Schnitzer T. DUROLANE International Study Group. *Osteoarthritis Cartilage*. 2004; 12: 642-9.

FIGURE 4 | Comparison of the Reduction in WOMAC Pain at the 40% and 50% Thresholds



*Gel-One not measured at 6 months.

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index. Adapted from Chevalier X, et al. *Ann Rheum Dis*. 2010; 69: 113-9; Anika Therapeutics, Inc. Clinical Data Analysis Report for MONOVISC. M. Frank-Molnia, Mar 2012. Data on File; Gel-One Summary of Safety and Effectiveness (Mar 21 2011). P080020. http://www.accessdata.fda.gov/cdrh_docs/pdf8/P080020b.pdf; Altman RD, Akermark C, Beaulieu AD, Schnitzer T. DUROLANE International Study Group. *Osteoarthritis Cartilage*. 2004; 12: 642-9.

TABLE 1 | Comparison of Hyaluronic Acid Formulations

	Monovisc	Synvisc-One	NeoVisc Single Dose	Durolane
Formulation	Cross-linked sodium hyaluronate	Hylan G-F 20	Sodium hyaluronate 1%	Stabilized HA (NASHA, or minimal cross-linking)
Indication	OA of the knee	OA of the knee	Synovial fluid replacement after arthrocentesis	OA of the knee and hip, ankle, fingers and toes (other posology)
Administration	Single injection	Single injection	Single injection	Single injection
Volume	4 mL	6 mL	6 mL	3 mL (for knee OA)
HA concentration	20 mg/mL	8 mg/mL	10 mg/mL	20 mg/mL
Chemically Modified	No	Yes	Yes	No
Total HA delivered per injection	80 mg	48 mg	60 mg	60 mg
Source	Non-avian	Avian	Non-avian	Non-avian

The disparate properties of current HA formulations underlie current efforts to isolate variables meaningful to sustained symptom control. While the same properties may be relevant to joint protection, identifying the most advantageous formulation at an optimal molecular weight and dose has brought HA through several generations. The ability of currently available single injections to provide pain relief for up to six months may be tied to molecular events that trigger relatively durable anti-inflammatory and anti-nociceptive effects.[32,33] Extending these effects present a target for therapies that will improve long-term outcome.

Conclusion

Exogenous HA products have been marketed for the treatment of OA for more than 15 years. Efforts to improve on exogenous HA therapy have generated an array of products with characteristics potentially meaningful to both safety and efficacy. Non-avian derived HA, for example, circumvents risk of allergic reactions, while high molecular weight products are credited with providing longer duration of action. Increasing the dose of HA has the potential for further extending activity and improving binding to CD44, the chondrocyte receptor by which HA may mediate both its viscoelastic properties and its homeostatic effects on joint integrity. The differences between products provide a basis for the experimental and clinical studies that will better define the most important activities of HA in regard to OA therapy.●

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Guest Editor

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Hyaluronic Acid in Clinical Practice: Managing Symptoms in Knee Osteoarthritis

The therapeutic goals in the management of osteoarthritis (OA) of the knee are to control pain and minimize functional limitations. Treatment is individualized with attention to the immediate objective of pain control while minimizing the risks of the prolonged therapies that may be required to control this chronic condition. Of pharmacologic therapies available for the treatment of knee OA, injection of hyaluronic acid (HA) offers a favorable balance of efficacy and safety. Unlike other conservative treatment options with efficacy against OA pain, such as non-steroidal anti-inflammatory drugs (NSAIDs), localized delivery of HA is associated with a low risk of local or systemic adverse effects. New generation HA therapies, relative to HA formulations introduced in Europe and the United States in the late 1990s, have several relative advantages, including a long duration of effect after a single injection and in some cases a more rapid onset of pain control. Characteristic differences among new generation agents may be further relevant to individualized care in selected patients.

Background

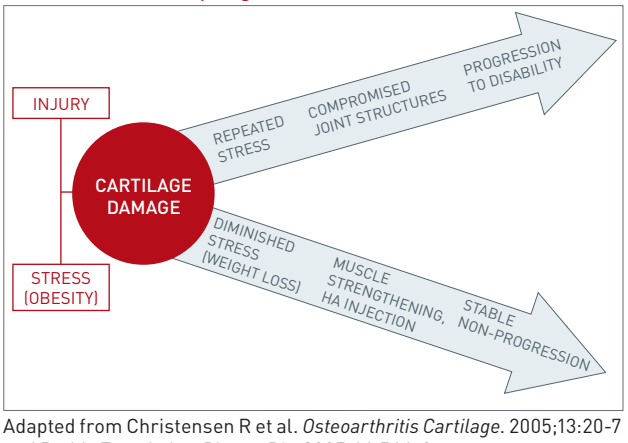
Osteoarthritis (OA) is often misunderstood as a condition of older individuals. Although deterioration of the cartilage leading to OA can be age-related, there are a broad number of etiologies that initiate the progressive events that characterize this condition. Currently, the median age at diagnosis of OA is 55,[1] but knee injuries that damage cartilage, ligaments or menisci, upsetting the balance of interrelated joint structures that drives progressive OA, can occur at any age.[2] The altered biomechanics of a limb can produce uneven stress on the joint causing early degeneration. Not all knee injuries lead to OA, which is multifactorial and may include a genetic predisposition,[3] but a variety of stresses to the knee, including injury, markedly increase risk.[4] Clinical knee OA may evolve a decade or more after a single index injury,[5] but early trauma or stress to the knee means that OA rates begin climbing in the third decade of life with case reports common at earlier ages.[6]

With evidence that knee OA can develop after traumatic knee injury, substantial attention has been paid to the risk posed by athletic injuries for early onset OA. In a review of the relationship between surgically-repaired anterior cruciate ligament (ACL) tears and knee OA, for example, it was concluded that isolated injuries pose a low risk, but risk of OA climbs markedly among those with both an ACL tear and another structural knee injury.[7]

However, traumatic injury is not the only insult that leads to initial degradation of articular cartilage. Obesity, which is increasingly common in many countries, including Canada,[8] is also associated with increased risk of early onset OA.[9] The biomechanical stress imposed by obesity on the knee is substantiated by reports of articular cartilage damage in obese teenagers.[10] In addition to stress, obesity, a pro-inflammatory condition, may further exacerbate joint equilibrium by upregulating factors contributing to OA pathology.[11]

The treatment of knee OA in relatively young patients underscores the challenges of balancing efficacy and safety over prolonged periods, which is an issue that may be equally relevant to an older population. Long-term treatment strategies are necessary, because OA is typically incurable and progressive. The speed at which OA progresses varies substantially,[12] but damage in most patients eventually extends to other joint tissues, including the synovial membrane, muscles, ligaments, and bone.[13] Non-pharmacological therapies, such as weight loss in the obese or muscle strengthening in those with traumatic injuries, are an important adjunct for slowing or halting OA progression.[14,15] While the immediate objective is pain relief and restoring or improving joint function, a combination of pharmacologic and non-pharmacologic interventions should be targeted at achieving stable, non-progressive disease (Figure 1).

FIGURE 1 | Steps toward Progression and Non-progression



Adapted from Christensen R et al. *Osteoarthritis Cartilage*. 2005;13:20-7 and Roddy E et al. *Ann Rheum Dis*. 2005;64:544-8.

Knee Osteoarthritis: Clinical Goals

Relative to clinical findings alone, radiographic studies are useful for improving the accuracy of the diagnosis of knee OA,[16] but there is a poor correlation between symptoms and radiographic severity as judged with the widely used Kellgren and Lawrence Classification system.[17] From the more practical clinical perspective in patients with established knee OA, reproducible methods developed for evaluating the clinical burden of knee OA may be useful. The Western Ontario and McMaster Universities Arthritis Index (WOMAC), which measures pain, stiffness, function, and global symptomatology, is accurate,[18,19] but many clinicians may be comfortable guiding or modifying treatment plans on the basis of patient report alone.

Due to the variability in the manifestations of OA, clinical goals may differ. Although knee OA is the leading cause of disability in Canada and the United States,[20,21] the definitions of disabling pain and joint stiffness are subjective. Regaining function may be a more important goal for an athlete with early onset OA and stiffness than an elderly individual whose dominant complaint is pain. However, the risk of adverse events from chronic treatment regimens is an issue for both. In relatively young patients, attention must be paid to disease control over decades. In the elderly, treatment selection requires sensitivity to the greater relative susceptibility of patients in this age group to acute adverse events.

OA at the present time cannot be cured, but there is interest in management that will slow or halt the biomechanical and biochemical events triggered by cartilage loss. These events include inflammation, joint destabilization, changes in joint alignment, and bone remodeling.[22] The only proven strategies to achieve this goal are non-pharmacologic

interventions, such as weight loss in the obese, that reduce injury to the articular cartilage. Novel treatments on the horizon, such as cell-based strategies to regenerate cartilage, [23] are driven by the goal of improving joint integrity to slow OA progression.

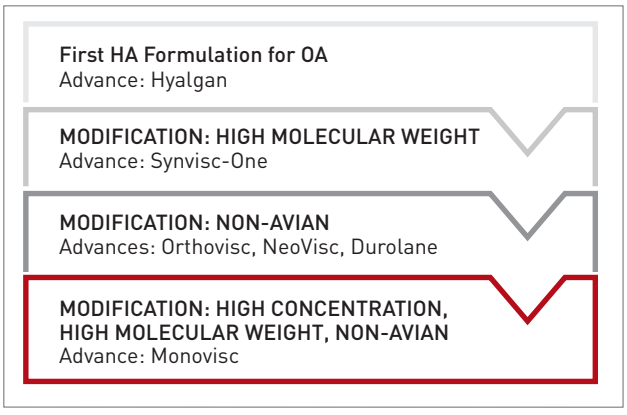
HA Injection in Control of Osteoarthritis

Injection of hyaluronic acid (HA), also called viscosupplementation, has been available in Canada for the treatment of knee OA for more than 10 years. Although only one option on a long list of pharmacologic therapies ranging from acetaminophen to opioids, it has been identified by the American Academy of Orthopaedic Surgeons (AAOS) as helpful for individuals with knee OA who have not responded to non-pharmacologic conservative measures or other basic treatments, such as acetaminophen. [24] The AAOS guidelines, which recommend HA for mild to moderate knee OA, note that HA is a naturally-occurring lubricant that is generally found in diminished concentration among patients with OA. Consistent with previously-published studies, [25, 26] the benefit from HA, as described by the AAOS, is derived from facilitating movement of knee joint components while improving shock absorption characteristics.

A review of 76 published studies with HA in the treatment of OA, of which 36 were against such active comparators as intra-articular corticosteroid injections, non-steroidal anti-inflammatory drugs (NSAIDs), and exercise, concluded that HA is effective with benefit on pain, function, and patient global assessment. [27] The authors further determined from this analysis that HA has a more prolonged clinical benefit than intra-articular corticosteroids, is as at least effective as most other pharmacologic therapies, and in general is associated with a low risk of systemic effects. However, they cautioned that there appears to be time-dependent and efficacy variability across products.

This variability is consistent with incremental advances in HA formulations. All of the initial formulations delivered HA in relatively low concentrations requiring multiple injections. Initial products were also of avian derivation. Subsequent HA formulations have been modified to increase duration of activity, reduce risk of adverse events, and to recreate a closer match to the biochemical activity of naturally-occurring HA, which plays a more active role in joint homeostasis than originally presumed (Figure 2). [28] Although the contribution of HA to the viscoelastic properties of synovial fluid were an initial impetus to develop exogenous products, [29] there is a large and growing body of clinical and experimental evidence that HA may also ameliorate knee OA pain and function by modifying pain perception, [30] upregulating of inflammatory mediators, [31] and preventing remodeling of extracellular matrix. [32]

FIGURE 2 | Advances in Hyaluronic Acid Formulations since Initial Introduction

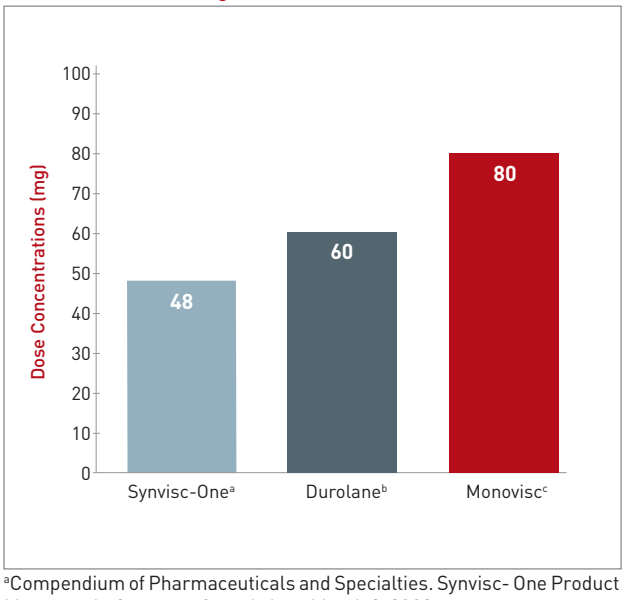


Adapted from Moreland LW. *Arthritis Res Ther.* 2003;5:54-67.

The optimal composition of HA has not been defined, but there is evidence that high molecular weight HA, which more closely approximates the endogenous form, provides greater bioactivity in OA patients than lower molecular weight formulations. [33] Recently, high molecular weight was found to provide greater joint lubrication in an experimental model. [34] The new generation HA products have been formulated therefore with higher molecular weights than the initial products.

More recent products have also been more likely to be derived from non-avian sources, avoiding the potential risks from allergies to poultry and egg proteins. Finally, the most recent products are employing higher concentrations, with the potential to increase the bioactivity of treatment, accelerate symptom control, and increase the duration of response. Of the most commonly used products, for example, Monovisc is injected in a dose of 80 mg whereas Synvisc-One is injected in a dose of 48 mg (Figure 3).

FIGURE 3 | Latest Hyaluronic Acid Formulations Use Higher Concentrations



[a]Compendium of Pharmaceuticals and Specialties. Synvisc- One Product Monograph, Genzyme Canada Inc., March 2, 2009.
[b]Durolane website. www.durolane.com (Accessed January 13, 2014).
[c]Monovisc Package insert, PENDOPHARM, March 2013.

There are no large, randomized, double-blind studies comparing available HA formulations, but the relative effects of single agent, placebo-controlled trials are consistent with the anticipated advantages of high molecular weight, high concentration agents. In the registration trials with Monovisc, for example, there was a 36.4% improvement in pain scores at the week 2 visit,[35] which has not been reported for other agents. WOMAC pain scores continued to decline over a subsequent 18-week period with scores still suppressed below the 2-week decline at the end of 26 weeks (Figure 4). The relatively rapid pain relief has important implications for the patient's ability to appreciate the efficacy of HA and its effect on quality of life.

FIGURE 4 | WOMAC Pain Scores: Effective OA Pain Relief with Onset at Two Weeks

ITT population n=181; WOMAC: Western Ontario and McMaster Universities Arthritis Index. Adapted from Anika Therapeutics, Inc. Clinical Data Analysis Report for MONOVISC. M. Frank-Molnia, Mar 2012. Data on File.

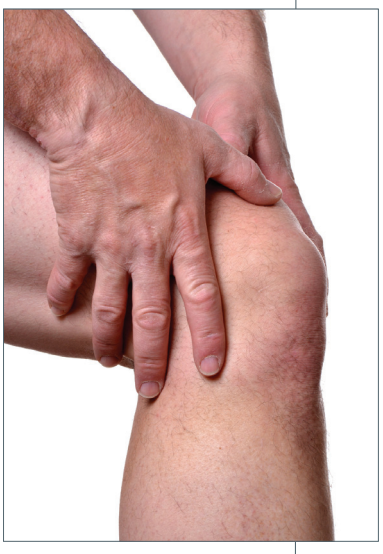
HA treatment is attractive for symptom control in mild to moderate disease when extended treatment encourages use of a well-tolerated therapy with a low risk of systemic effects. With current high molecular weight and high concentration formulations, single injections may provide efficacy for periods of up to six months, circumventing the inconvenience and discomfort of frequent retreatments. In addition to HA therapy it is recommended that patients also receive adjuvant strategies. These include muscle-strengthening exercises in the context of physical therapy and knee bracing. While long-term benefit from braces has not been demonstrated in a controlled trial, this approach has been shown to reduce joint loading and improve gait symmetry.[36] In some patients, particularly those unable or unwilling to complete physical therapy, patients should also be counselled to modify activity to reduce stress on the damaged joint.

Conclusion

OA of the knee is a challenging condition for which the immediate goals of therapy must be considered in the context of risk of progression and long-term management. HA is one of many options, but its attributes include a level of symptom control at least comparable to NSAIDs and intra-articular steroid injections. Replacing an endogenous compound important to joint kinetics, exogenous HA also poses a low risk for systemic side effects. Newer non-avian formulations with a high molecular weight and high concentration may better reproduce the activities of HA in the joint relative to earlier generation products. When combined with non-pharmacologic interventions, HA may be a valuable tool in the effort to achieve sustained relief of pain, improve function, and reduce risk of disease progression.●

CASE 1

35-Year-Old Male



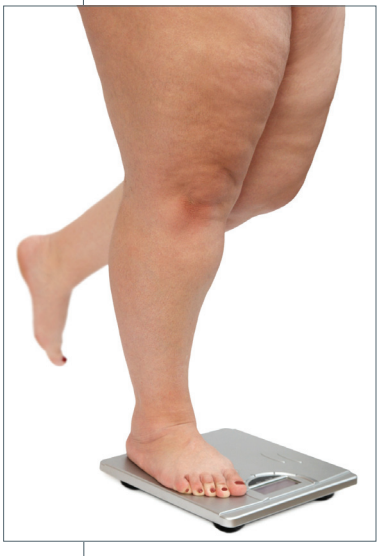
An otherwise fit accountant with a history of increasing knee pain provides a history of joint stiffness that is limiting his ability to pursue recreational skiing. He has self-medicated with ibuprofen to control symptoms but reports frequent episodes of dyspepsia. A diagnosis of OA is made on the basis of classic clinical signs.

- Although patient is initially referred for strengthening exercises, persistent pain brings the patient back for additional symptom control.
- High molecular weight, high-concentration HA is injected with instructions to avoid high-intensity exercise for 48 hours and to monitor swelling.
- In a telephone follow-up 2 weeks after injection, patient reports symptom improvement but is still supplementing treatment with ibuprofen.
- Four weeks after therapy, patient removes himself from supplemental analgesics and intensifies strengthening regimen.
- Patient is instructed to return in 6 months, or earlier if symptoms recur.

CASE 2

60-Year-Old Female

Recently retired after 30 years of a demanding work schedule, a former real estate saleswoman's adoption of a sedentary lifestyle has led to a body mass index (BMI) increase from 32 to 37 in just two years. She has type 2 diabetes and hypertension. Her many allergies include nuts, eggs, and tomatoes. Her prior history includes a gastrointestinal bleed. Upon radiological examination, the patient meets Kellgren and Lawrence criteria for grade 2 OA.



- Relatively contraindicated for a COX-2 inhibitor because of cardiovascular risk factors, the patient has self-medicated with opioid analgesics obtained for a prior foot injury and complains of poor daytime concentration.
- Trial of a high molecular weight, high-concentration, non-avian HA is initiated.
- Patient is instructed to take acetaminophen for pain control.
- In follow-up at two weeks, patient reports insufficient pain control and requests opioid. She accedes to recommendation to wait an additional two weeks, but remains non-compliant to weight loss recommendation.
- Pain control at three weeks is adequate but radiograph at 6 months shows substantial joint deterioration to Kellgren and Lawrence grade 3.
- Surgical options are considered.

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