

## Viscosupplementation for Treating Osteoarthritis in the Military Population

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**ABSTRACT** Military personnel have a greater risk of developing osteoarthritis (OA) than the general population. OA is a chronic, painful, and debilitating disease with a high cost burden. Compared with the general population, a higher prevalence of post-traumatic OA has been reported in the military. Using recent literature, we aim to improve the understanding of post-traumatic OA, with an exploration of the pathophysiology of OA. Our review encompasses the current treatment modalities for alleviating the pain from OA with a focus on viscosupplementation. A multimodal approach may be beneficial for the relief of OA pain and improvement of function in military personnel with early OA, and may lower the cost burden.

### METHODS

Relevant literature on osteoarthritis (OA) in the military and OA treatments used to alleviate OA pain were identified through PubMed database searches from inception until January 2013. Specific search terms included military and OA. OA treatments, including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), duloxetine, opioids, and intra-articular steroids and hyaluronic acid (HA) injections, were also included as keywords. Overviews of these OA treatment options are discussed, with an emphasis on the efficacy and safety of viscosupplementation.

### MILITARY POPULATION PROFILE

Osteoarthritis (OA) is endemic within the military and veterans' populations.<sup>1</sup> The primary reasons for this are the extreme activities and demands of this unique population. Our military personnel have strict mandatory physical exercise requirements, as well as the frequent need to perform in extreme environments bearing loads that exceed normal physiologic ranges. This active cohort is at risk of athletic knee injuries at an order of magnitude greater than the civilian population.<sup>1-3</sup>

Articular injuries have been shown to progress toward early OA.<sup>4</sup> Rivera and colleagues<sup>3</sup> reported that OA is the primary source of disability discharge in our military person-

nel, with 94.4% of the OA being attributed to combat injury, occurring at an average of 19 months after injury. To address the burden of OA, a recent American Academy of Orthopaedic Surgeons (AAOS) Extremity War Injury Symposium brought together military and civilian orthopedic surgeons as well as researchers and determined that one of the most significant sequelae of extremity injuries is the burden of post-traumatic OA.<sup>5</sup> Collectively, this evidence underscores the need for continued study of post-traumatic OA, as well as surgical and medical treatments to help retard the progression of OA and control the symptoms in the military population.

### OA INTRODUCTION

Initial degradative changes in articular cartilage are typically silent. However, once symptoms appear, OA is a chronic, progressive condition<sup>6</sup> that causes pain and increasing disability.<sup>7</sup> After accounting for mechanical disorders, OA has a high rate of comorbidities (67%) in the general population, including diabetes and obesity.<sup>8</sup> Over the past decade, increasing interest in these comorbidities has led to an association of OA with cardiovascular disorders and hypertension.<sup>8,9</sup> The term "metabolic syndrome" has been applied to the combination of obesity, diabetes, hypertension, and cardiovascular disease.<sup>9</sup>

A study of the personnel in the Brazilian Navy found 30% of members had two or more risk factors (abdominal obesity, low HDL cholesterol, high fasting glycemia, high triglycerides, high blood pressure) for metabolic syndrome.<sup>10</sup> In Finland, the high prevalence rate of metabolic syndrome in young obese men decreased by 40% with the physical exercise required with military service.<sup>9</sup> With such a high rate of comorbidities, OA is a serious public health concern, and with the high numbers of combat injuries leading to

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post-traumatic OA, the expenditures from OA-related health care costs for disabled troops are rising.

The current Department of Defense (DoD) expenditure for medical care of the active duty and veteran population is 9% of the DoD entire budget.<sup>11</sup> Expenditures for health care are projected to continue consuming increasing portions of the DOD budget impacting budgets for training, maintenance, and acquisition of new weapons platforms. High health care costs for OA have been reported for the general population.<sup>12</sup> As orthopaedic and musculoskeletal system conditions are the leading cause of disability in the Army and Navy,<sup>13</sup> OA health care expenses will adversely impact the military budget.

Although OA incidence is known to increase with age, OA incidence is rising more rapidly for the military compared with the general population, with the rate more than double for military personnel 40 years and older.<sup>1</sup> The OA incidence rates for women in the military are higher than men in the military, and African American troops have a higher incidence of OA than Caucasians.<sup>1</sup> Understanding the synergism between mechanical and systemic factors contributing to OA in the military population is key to the selection of the most appropriate interventions. In this review, we summarize potential OA treatments, with an emphasis on using viscosupplementation to alleviate knee OA pain.

## **OA PATHOPHYSIOLOGY**

Molecular, mechanical, and traumatic events can all predispose a person for OA.<sup>14</sup> Genetic factors and the effects of aging can also play a role.<sup>6</sup> OA is considered a disease of the whole joint, affecting all joint tissues as they communicate with each other by releasing and responding to various signaling molecules.<sup>15</sup> Although the major molecules of articular cartilage are collagen and aggrecan,<sup>7</sup> chondrocytes are the unique cells in cartilage that maintain joint homeostasis.<sup>15</sup> OA is typically characterized by degradation of type 2 collagen, a decrease in the amount and size of aggrecan, and the diminished ability of chondrocytes to remodel and repair the cartilage matrix.<sup>6</sup> With the disruption of type 2 collagen and loss of aggrecan, water content in the joint increases and the cartilage matrix loses tensile strength.<sup>6</sup> When responding to inflammation and stress, osteoarthritic chondrocytes produce matrix-degrading enzymes, which further disrupt the joint matrix environment.<sup>15</sup> These molecular changes to the cartilage reduce the ability of cartilage to disperse the load, minimize friction, and allow movement of the joint.<sup>16</sup>

Other joint factors besides the cartilage also appear to contribute to the osteoarthritic process. The elasticity of synovial fluid, which lubricates and protects the knee joint, decreases with age and is more dramatic with OA.<sup>17</sup> The fluid of the knee joint is viscous, in part, because of the HA content; but in OA, the knee has about half the amount of HA as a healthy adult knee.<sup>17</sup> Intuitively, less synovial fluid should cause an increase in the friction coefficient,<sup>18</sup> which would compromise the ability of the synovial fluid to lubricate and protect the joint. Recently, Caligaris and colleagues demon-

strated that the friction coefficient of human tibiofemoral cartilage did not increase with increasing grades of OA, but did increase with decreasing molecular weight of osteoarthritic synovial fluid.<sup>18</sup> From a scientific viewpoint, they concluded that intra-articular injections of high molecular weight synovial fluid may produce a statistically significant decrease in the cartilage friction coefficient.<sup>18</sup>

Mechanical factors also contribute to OA through joint instability and misalignment.<sup>6</sup> Muscular weakness, such as from the quadriceps muscle, can increase OA progression, secondary to decreased joint stability and the inability of the muscle to assist with shock absorption of the joint during gait. Military populations require high activity levels that demand increased use of the knees, placing troops at a higher risk for knee injuries.<sup>2</sup> In the general population, lifetime risk of developing OA is significantly higher for those with a history of knee injury (57%) compared with those without knee injuries (42%).<sup>19</sup> In a recent study of post-traumatic OA in the military, Rivera and colleagues noted that all warriors (100%) who sustained knee injuries, subsequently developed OA.<sup>3</sup>

Altered mechanics because of injury may be direct or indirect. Direct articular cartilage impact can disrupt the knee meniscus, ligaments, cartilage, and bone.<sup>4</sup> The long-term effects of cruciate and major meniscal injury are well known.<sup>4</sup> Even with surgical repair, a disrupted anterior cruciate ligament could not restore knee kinematics and joint contact mechanics.<sup>20</sup> Because the military is such a physically active population, the 10 times greater incidence rate of anterior cruciate ligament injuries reported for military personnel compared with other nonmilitary populations is not unexpected.<sup>2</sup> Jones and colleagues reported that incidence for meniscal injury increased approximately 60% for every 5-year age group.<sup>2</sup> In fact, approximately 50% of patients who underwent meniscal surgery developed knee OA within 10 to 20 years.<sup>4</sup>

Cellular changes accompany the mechanical changes to the joint that occur with injury.<sup>21</sup> Following sublethal injury to chondrocytes, the combination of apoptosis and mechanically driven shifts in chondrocyte phenotype leads to stress-induced signaling cascades and activation of inflammatory mediators.<sup>15,21</sup> Other genes involved in injury response include protein kinases that promote apoptosis.<sup>21</sup> The joint's response to injury will vary based on which genes are activated, but the increased expression of inflammatory and apoptotic signals can lead to more rapid articular cartilage degradation.<sup>15,21</sup> Thus, cellular responses to injury induce inflammatory responses that in turn perpetuate cartilage degradation and weaken the ability to repair the joint.<sup>15</sup> These changes are likely to further contribute to the development and progression of OA.<sup>15</sup>

To reduce the impact of post-traumatic OA, current research efforts are examining ways to preserve and protect the joint, to repair damaged articular cartilage, and to prevent cell death after injury.<sup>5</sup>

Pain from OA is a potent motivator for people to seek treatment for their OA. Patients typically describe pain that begins gradually and worsens over time. The pain in the joint is not produced from the cartilage because cartilage does not have any nerve endings.<sup>22</sup> With movement, joints send signals to sensory nerves.<sup>6</sup> In OA, the signaling is increased, and is interpreted as pain in the central nervous system.<sup>6</sup> Discomfort from OA is often hard to localize for patients. They may have OA in one portion of the joint, but perceive the pain radiating to the other side of the joint, or up and down the leg.

Synovial inflammation may further promote cartilage destruction or hinder the ability of cartilage to be repaired.<sup>15</sup> The resulting swelling can be very painful, and may decrease the range of motion of the joint. Interestingly, this may be protective. Many patients will rest and reduce their activity level because of the swollen joint, which decreases potential damage to the joint.

OA is progressive and will continue to worsen with time. Although the disease will progress, treatment can help alleviate OA pain and may be able to slow the progression.

**OA TREATMENTS**

Although the U.S. military does not have a defined treatment algorithm for OA, traditional treatment algorithms have been presented as a pyramid.<sup>23</sup> Professional society guidelines, such as from the American College of Rheumatology and the Osteoarthritis Research Society International, are usually followed.<sup>24,25</sup>

Initial treatment options for OA are simple (Table 1). Often, simply resting the joint and avoiding high-impact loading activities can lessen the pain and swelling. By decreasing swelling of the joint, the knee is more likely to function more normally and not feel unstable.

Other nonpharmacologic treatment options that are recommended include exercise, weight loss, and physical therapy.<sup>24,25</sup> Pharmacologic interventions include acetaminophen; nonsteroidal anti-inflammatory drugs, including cyclooxygenase inhibitors; duloxetine; opioids; intra-articular steroid; and viscosupplement injections.<sup>24,25</sup>

**TABLE I.** Treatments for Osteoarthritis

Nonpharmacologic
Rest
Exercise
Weight loss
Physical therapy
Pharmacologic
Acetaminophen
NSAIDs
Duloxetine
Opioids
Intra-articular Steroids
Viscosupplements
Multimodal Treatments

Current treatment algorithms are based on starting only one therapy, and progressing to the next if the first therapy is not successful or is not well tolerated.<sup>23</sup> By using only one therapeutic at a time, treatment for OA may be suboptimal. However, most of the studies published to date describe a therapeutic intervention compared with placebo, and thus the data on multimodal treatment are sparse. In the following sections, we will briefly cover pharmacologic treatment options for OA.

**Acetaminophen**

Although acetaminophen is readily available, studies have shown only a modest effect size (standardized mean difference, -0.13; 95% confidence interval, -0.22, -0.04) for alleviating pain associated with OA compared with placebo.<sup>26</sup> Most of the studies included in this meta-analysis compared 4 g daily dosing of acetaminophen with placebo.<sup>26</sup>

**Nonsteroidal Anti-Inflammatory Drugs**

NSAIDs are also often prescribed to reduce knee OA pain. Nonselective NSAIDs, such as ibuprofen, naproxen, and aspirin, inhibit cyclooxygenase-1 (Cox-1) and cyclooxygenase-2 (Cox-2) enzymes. Cox-1 enzymes are protective of gastrointestinal (GI) tract, whereas Cox-2 enzymes are involved in inflammation.<sup>27</sup>

Chronic use of NSAIDs is not recommended because of the reported risk of adverse cardiovascular and GI events.<sup>27</sup> Cox-2 specific inhibitors were developed to decrease adverse gastrointestinal effects and were introduced in the United States in 1999. Although celecoxib, the only selective Cox-2 inhibitor currently available in the United States, has been shown to have a lower incidence of GI events compared with nonselective NSAIDs, all NSAIDs carry a boxed warning describing cardiovascular and GI risks.<sup>27</sup>

**Duloxetine**

Although many of the other pharmacologic treatments used to alleviate OA pain target the peripheral nervous system, duloxetine is a serotonin-norepinephrine reuptake inhibitor and acts on the central nervous system.<sup>28</sup> Duloxetine is indicated for chronic musculoskeletal pain,<sup>29</sup> although only short-term efficacy has been shown in clinical trials.<sup>28</sup> The boxed warning on the prescribing information notes the potential for an increased risk in suicidal thinking and behavior in young adults.<sup>29</sup>

**Opioids**

Prescription narcotics are not generally recommended to treat mild to moderate OA. Weak opioids and tramadol are indicated for treating refractory OA pain when other medications have been ineffective or are contraindicated.<sup>24,30</sup> The efficacy of opioids decreases after 3 to 4 weeks, and are limited because of the risk of addiction and a high frequency of undesirable side effects.<sup>31</sup> Tramadol is a weak opioid that is

indicated for the management of moderate to severe pain.<sup>32</sup> As with other opioids, tramadol can develop tolerance, and carries significant warnings of increased risks of adverse reactions on its prescribing information.<sup>32</sup>

### **Intra-articular Steroids**

Intra-articular corticosteroid injections are effective for short-term pain relief with an effect size of 0.72 at 1 week waning to 0.21 by 6 weeks.<sup>25</sup> Most of the reported side effects are localized to the intra-articular injection site.<sup>33</sup>

### **Viscosupplements**

Intra-articular injection of viscosupplements (hyaluronan; HA) provides lubrication and has been shown to lower the friction coefficient.<sup>18</sup> Viscosupplements can be used to treat knee OA pain. Because HA is a major component of synovial fluid and is found at decreased levels in the OA knee, intra-articular HA injections can be used to supplement endogenous HA. In the United States, intra-articular HAs have been used as a knee OA treatment since 1997 with pain relief up to 6 months.<sup>34</sup>

Recent AAOS Guidelines have indicated concern for the use of HA treatment for knee OA.<sup>35</sup> However, these guidelines do not define the use of HA in an active population, such as active duty personnel.

Intra-articular injection of HAs may reduce knee OA pain by inhibiting nociceptors, stimulating endogenous HA, inhibiting matrix-degrading enzymes, and through anti-inflammatory mechanisms.<sup>7</sup>

Typical regimens for viscosupplements have required cycles of 3 to 5 injections in the knee, which may increase the opportunity for injection-related adverse events.<sup>36</sup> Recently, two viscosupplements are indicated for alleviating OA pain in one injection, and can provide 13 weeks<sup>37</sup> to 26 weeks<sup>38</sup> of pain relief. A single injection protocol also reduces the need for multiple office visits. The most common adverse effects with viscosupplementation are transient local pain and swelling at the injection site.<sup>37,38</sup>

Repeat cycles of viscosupplements have reported sustained improvements. Total knee replacement may be delayed for up to 4 years.<sup>39</sup> Some studies have reported similar adverse events,<sup>40,41</sup> whereas others have noted a slight increase in local adverse events with repeat injections.<sup>42,43</sup>

Several studies have suggested a need for earlier interventions for post-traumatic OA.<sup>21,44</sup> Also, a potential disease-modifying effect with viscosupplement therapy has been suggested.<sup>45</sup> Viscosupplements have been shown to be more effective in earlier stages/grades of disease, more recently diagnosed OA, and in less severe radiographic OA.<sup>46</sup>

The role of viscosupplements in the perioperative management of knee internal derangement is unclear. Although improved surgical outcomes have been reported when viscosupplements are added to the postsurgical treatment plan,<sup>47-49</sup> one study has shown no efficacy compared with bupivacaine.<sup>50</sup>

### **MULTIMODAL OA TREATMENT**

In the past few years, many publications have demonstrated that the traditional algorithm for the management of OA may be inadequate. In this section, we present the need for multimodal treatment and show that combination therapy may reduce costs as well.

Several studies have shown viscosupplementation combined with appropriate care, conventional therapy, or exercise is more effective compared with other therapies alone.<sup>34</sup> Also, a combination of viscosupplements with other pharmacologic agents, such as NSAIDs or corticosteroids, may be beneficial, although concomitant use has not been rigorously tested. If an adverse event occurred, it would be impossible to determine the cause. However, combining viscosupplements with NSAIDs showed better outcomes than NSAIDs alone.<sup>51</sup> A recent study by de Campos and colleagues found a combination of a viscosupplement with a corticosteroid improved pain scores for the first week compared with the viscosupplement alone, although the benefit of combined therapy did not continue after the first week.<sup>52</sup>

Some studies have shown that viscosupplementation can decrease the need for additional analgesics, which may reduce the overall cost of treatment.<sup>46,53,54</sup> A study reported that most patients injected with viscosupplementation were able to discontinue or use fewer analgesics, NSAIDs, and glucocorticoids.<sup>53</sup> Kahan et al calculated cost of treatments for OA pain relief.<sup>54</sup> They found patients using viscosupplementation compared with patients using conventional treatments had similar total medical and nonmedical costs.<sup>54</sup> Another study by Zhang and colleagues found that the annual cost of viscosupplementation was cheaper than NSAIDs.<sup>55</sup>

Because of the low incidence of side effects, viscosupplementation may help older reserves being called for active duty, and may offer a faster return to active duty after knee injuries or knee surgeries.

### **CONCLUSIONS**

Treatments for OA are used to manage the pain, and some therapeutics may slow the progression. Most treatment regimens initially begin with exercise plans, physical therapy, and weight loss. Simple analgesics, such as acetaminophen and NSAIDs, may be prescribed if needed. When these treatments fail to successfully alleviate pain, opioids and intra-articular injections of corticosteroids or viscosupplements may be used. Some reports have shown that many patients with mild to moderate OA of the knee can be managed for long periods of time with a conservative multimodal approach. Physical therapy, nutritional counseling, and pharmacotherapeutics can be used concomitantly with a high likelihood of increased efficaciousness, but with nominal adverse events. This review highlights studies showing the benefit of a multimodal approach that includes viscosupplementation. A multimodal approach for the treatment of OA of the knee with viscosupplementation provides good efficacy for pain relief

and return to function when used in an active population; however, further research in larger studies is warranted.

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