GLUCOSAMINE AND CHONDROITIN SUPPLEMENTATION IN ATHLETES TO PREVENT THE EARLY ONSET OF OSTEOARTHRITIS FOLLOWING KNEE INJURY

LITERATURE REVIEW

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Glucosamine and Chondroitin Supplementation in Athletes to Prevent the Early Onset of Osteoarthritis Following Knee Injury: A Literature Review

The purpose of this literature review is to explore the research on Glucosamine and Chondroitin as it relates to treatment of osteoarthritis, what the demonstrated symptomatic and structural effects of these dietary supplements are, and the safety of long-term supplementation. Further, how does this research relate to the world of sports medicine, the treatment of injuries, and prevention of degenerative disease like osteoarthritis down the road? Studies involving athletes who had an Anterior Cruciate Ligament (ACL) tear of the knee, showed that on average 50% of these athletes experienced an early onset of osteoarthritis 10-20 years post injury (Lohmander, Englund, Dahl & Roos, 2007). Based on the strong correlation between injury and early onset of osteoarthritis, should we supplementing our young adult athletes with Glucosamine and Chondroitin in hopes of preventing osteoarthritis before it sets in?

Nutritional supplements are meant to supplement diets that are lacking in certain nutrients and/or food groups, or for individuals with deficiencies. Aside from the reported health benefits of nutritional supplements, they are widely sold and marketed as enhancements for performance and strength training. The term "nutraceutical" is also commonly used in reference to a nutritional supplement with medicinal qualities. This term was coined by Dr. Stephen DeFelice at the Foundation for Innovation in Medicine (National Nutraceutical Center, 2005). A focus on preventative medicine, wanting to stave off the effects of aging, high medical costs and chronic disease with poor therapeutic management are some of the reasons why approximately 40% of Americans are using nutraceuticals (National Nutraceutical Center, 2005).

A recent study involving 145 Division I college athletes looked at attitudes towards supplement use for injury care. Interest in supplements was mild, however, 70% of the subjects identified their Athletic Trainer as the primary resource regarding information about supplementation (Malinauskas, Overton, Carraway & Cash, 2007). It is the role of the Athletic Trainer as a health care provider to ensure that proper care is being provided, but also that a preventative approach to injury care is implemented including proper strength and conditioning, safe training techniques, and optimal nutrition. Athletic Trainers provide a foundation of evidence-based information, which allows the athlete to make informed decisions about their healthcare, in order to prevent injury during competition. The goal of prevention in sports medicine is not only to prevent acute injuries, but to prevent chronic degenerative joint diseases such as osteoarthritis that occur later in life.

Literature Review

Osteoarthritis

Characteristics of OA. Osteoarthritis (OA) is characterized by the continual wearing of the articular cartilage. Lohmander et al. (2007) describes OA as a common, age-related, heterogeneous group of disorders characterized by focal areas of loss of articular cartilage in synovial joints associated with varying degrees of osteophyte formation, subchondral bone change, and synovitis. Additionally, OA is visible on plain radiographs as joint space loss, osteophytes, subchondral sclerosis, and bone cysts (Lohmander et al., 2007). While OA may be considered a disease of aging, age alone is not the only contributing factor. Other predisposing factors include gender—women more often than men, obesity, repetitive stress, muscle weakness, and poor joint design (Felson, 2004).

Cartilage is important to the joint and bone surfaces because it functions to distribute loads, minimize peak stresses on subchondral bone, and provide a friction reducing, and weight bearing surface (James & Uhl, 2001). It operates like a sponge soaking up water. Once the load has dissipated throughout the cartilage, the extracellular matrix (consisting of proteoglycans and glycosaminoglycans) works hydrophillically to absorb fluid back into the cartilage preparing it for another load (James & Uhl, 2001). Because cartilage is aneural, it cannot be the tissue that directly generates pain. Research suggests that subchondral bone and the synovium are responsible for nociceptive (pain) stimuli (Lohmander et al., 2007).

Early OA onset following ACL injuries. The current approach to prevention of early onset of osteoarthritis following traumatic injury, is typically surgical reconstruction of the torn ligament. The majority of American orthopedic surgeons believe that ACL reconstruction reduces the rate of OA in ACL-deficient knees (Lohmander et al., 2007). Reconstruction allows for restoration of the kinematics of the knee joint, thus hopefully decreasing focal stress on the cartilage. Kessler et al. (2007) followed patients who sustained an ACL tear over a period of 11 years. Out of 109 patients, 60 had ACL reconstruction, with the remainder undergoing conservative treatment. The surgical patients had higher scores with functionality in that 53% scored their function as “normal” vs only 14% with the conservative group. Conversely, 20% of the surgical patients scored their function as “abnormal” vs 31% of the conservative group. Overall, 52% of all patients did not have osteoarthritis at the time of follow up, however, there was significantly more patients with Grade II OA in the surgical group versus the conservative group (Kessler et al., 2007).

Potter et al. (2011) followed patients with ACL injuries over a 7-11 year period. Not all patients opted for an ACL reconstruction. Ultimately, among the 42 people involved in the

longitudinal study, whether or not the patient had a reconstruction did not impact the long term outcomes. Regardless if the patient had reconstruction or not, their risk for cartilage loss was 50 times higher for the lateral femoral condyle, 30 times higher for the patella, and 19 times higher for the medial femoral condyle (Potter et al., 2011). It was observed that non-surgical patients did have a higher risk of cartilage loss in the medial tibial plateau versus surgical patients. This study focused primary on early to middle adult aged patients, excluding patients over the age of 55.

Nebelung and Wuschech (2005) conducted a 35 year follow-up of prospective Olympic athletes, who sustained ACL tears but did not have a surgical fixation, and remained ACL deficient. The athletes were in their early to late twenties, and sustained their injuries from 1963-1965. Treatment included first aspiration of the hemarthrosis, and then plaster cast for up to six weeks of immobilization. A standard approach to rehab followed, and most of the athletes returned to competition within 14 weeks. In total, 19 athletes were involved in the study. Most retired from sport from one to four years following injury, many due to knee pain. Within 10 years of their injuries, almost 80% had to have a menisectomy. Only one individual was happy with their knee function, and 13 out of 18 subjects demonstrated advanced chondral lesions. In the end, after ~ 30 years, 95% needed menisectomies—26 arthroscopies in 17 patients—and 50% had total knee replacements. This study gives substance to the current approach to ACL surgical reconstruction in the hopes of preventing and/or limiting osteoarthritis and meniscus damage following injury.

In addition to ACL tears, research has also focused on meniscus injuries to the knee. The rates for the onset of OA post-meniscus injury are the same as ACL injuries. Overall, 50% of individuals who have a menisectomy eventually develop OA 10-20 years post injury. Further, it

is suggested that arthroscopic knee surgery to repair or remove degenerated and/or damaged meniscus will do little to influence the disease process in OA, or alleviate the symptoms that likely originate from other structures (Lohmander et al., 2007).

Safety of Glucosamine and Chondroitin

In general, Glucosamine and Chondroitin have been deemed relatively safe, with no known major adverse reactions. They can be found easily at any health foods or supplement store, and are widely marketed towards older adults who already suffer from osteoarthritis. Past and present research has focused primarily on how it either decreases pain/improves quality of life (symptomatic) or delays/reverses the degenerative process of osteoarthritis (structural effects). The National Institute of Health (2008) describes Glucosamine and Chondroitin as the following:

> Glucosamine and chondroitin sulfate are natural substances found in and around the cells of cartilage. Glucosamine is an amino sugar that the body produces and distributes in cartilage and other connective tissue, and chondroitin sulfate is a complex carbohydrate that helps cartilage retain water. In the United States, glucosamine and chondroitin sulfate are sold as dietary supplements, which are regulated as foods rather than drugs.

The primary concerns with supplements are manufacturing and safety. Glucosamine and Chondroitin are technically dietary supplements, meaning they are not regulated the same as medical drugs, but are viewed as a natural, alternative or homeopathic medicine. The Food and Drug Administration (2009a) passed the Dietary Supplement Health and Education Act in 1994, which puts the responsibility of safety of the supplement in the hands of the manufacturer. The manufacturer must ensure the supplement's safety, provide a complete ingredients list, but does not have to provide evidence of the claims made on how the supplement works.

Safety and health of the athlete is the primary concern, however, another concern is the potential of testing positive for a banned substance. Many of the governing bodies for collegiate sports have a banned substance list, and often regular and/or random drug testing occurs, especially during post season play. The National Collegiate Athletic Association (2013) offers this warning statement in regards to supplementation:

NCAA Nutritional/Dietary Supplements Warning:
Before consuming any nutritional/dietary supplement product, review the product with the appropriate or designated athletics department staff!

- Dietary supplements are not well regulated and may cause a positive drug test result.
- Student-athletes have tested positive and lost their eligibility using dietary supplements.
- Many dietary supplements are contaminated with banned drugs not listed on the label.
- Any product containing a dietary supplement ingredient is taken at your own risk.

This is a vague warning, and does not note specific supplements that may result in a positive drug test, but rather focuses on the fact that not all ingredients in the supplement may be on the label, so athletes could be inadvertently taking a banned substance.

While supplements might not be closely regulated for safety and potency, a risk assessment that looked at studies 12 weeks to three years in duration, supports the supplements' safety. There have been few documented serious adverse reactions to the supplements, with the exception that people who are allergic to shellfish, should avoid Glucosamine derived from shellfish. The relationship between glucosamine supplementation and diabetes has also been explored. It has been suggested that glucosamine supplementation possibly causes disruption to glucose homeostasis (Hathcock & Shao, 2007). However, a 12 week study involving human subjects and standard doses of glucosamine found no diabetogenic effects (Tannis, Barban & Conquer, 2004). There is No Observed Adverse Effect Level (NOAEL), meaning that there is no set dosage where adverse effects may be experienced—it would take a high amount of the

supplement to be toxic. Standard dosages for Glucosamine Sulfate are 1500 mg/day and Chondroitin Sulfate 1200 mg/day (Hathcock & Shao, 2007).

Currently there is no research involving the athletic population and supplementation with Glucosamine and Chondroitin as a preventative measure. The potential for risk (and cost) associated with unknown outcomes of long-term supplementation seem to make longitudinal studies un-justifiable. However, the sub set of athletes who experience early onset osteoarthritis provides an "alternative scenario" for research and treatment. Due to the fact that there is no evidence to support this type of treatment, it needs to be evaluated formally (Hunter & Hellio Le Graverand-Gastineau, 2008).

Symptomatic Effects

The primary controversy over Glucosamine and/or Chondroitin supplementation is in regards to how it works. Does it work structurally or symptomatically? Symptomatic effects may include alleviation of pain and stiffness, and improvement of function. Ultimately, in the greater context of treatment of a human medical condition, how a patient feels, functions or survives is the most important outcome (Lohmander et al., 2007). Is the drug or supplement "clinically meaningful" referring to whether it makes a meaningful impact on the quality of life and in particular physical function (Hunter & Hellio Le Graverand-Gastineau, 2008). The majority of the symptomatic based research utilizes the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) survey as an assessment tool. The WOMAC has three subscales: pain, stiffness, and function. The three subcategories asses how pain and function affect activities of daily life (ADLs) and how stiff a person is in the morning vs. later in the day (American College of Rheumatology, 2012).

Gait studies. Recently, the National Institute of Health (2008) funded a large-scale study called the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT). This study looked at both the symptomatic and structural effects of both Glucosamine and Chondroitin. While this research has not shown an overwhelming amount of support for the efficiency of these supplements, wide-spread subjective reporting of symptomatic relief has prompted this country-wide, multi-site research comparing it to standard anti-inflammatory medication(s) commonly used to treat OA.

The original GAIT study found that, while there was not an overall significant difference between placebo groups and control groups, there was a sub-group that experienced significant improvement in their symptoms. Participants received either 1500 mg/day of Glucosamine alone or in combination with 1200 mg/day of Chondroitin. Approximately 80% of the group in the moderate-to-severe stage of the disease reported a 20% or better improvement in their symptoms overall (Clegg et al., 2006). A follow up GAIT study found that Chondroitin had a significant effect on joint swelling vs placebo group. Over the course of a 24 week study, participants who took Chondroitin had reduced pain/stiffness scores, and improved function, secondary to decreased swelling. This was observed on participants with Kellegren-Lawrence Grade 2 radiographic changes, or moderate osteoarthritis (Hochberg & Clegg, 2008). A third GAIT study, lasting 24 weeks in duration, did not demonstrate any clinically important differences between Glucosamine/Chondroitin and placebo. A combination of Glucosamine and Celecoxib (Celebrex—NSAID) did, however, reduce WOMAC pain scores by 20% (Swatizke, et al., 2010).

Messier et al. (2007) followed the same basic guidelines as the GAIT study, however, this study also incorporated an exercise program after a 6 month supplementation period. This is

a mild simulation to athletes in competition, but not on the same scale as this program involved 3 days/week of mild-moderated controlled activity for six months, whereas competitive sports tends to be 5-7 days/week of intense, uncontrolled activity. Participants in the Glucosamine/ Chondroitin group improved by 17% with pain, and function scores vs placebo at 12%. Use of acetaminophen decreased by 37% in Glucosamine/Chondroitin group vs 11% in placebo group after 12 months (Messier et al., 2007). This might suggest that the Glucosamine/Chondroitin supplementation allowed for sustained physical activity and decreased pain medicine intake. Initially, the study did not find significant differences between Glucosamine/Chondroitin, however, post hoc analysis did find that the greater the compliance with supplementation, the greater the improvements in pain and function for participants in the Glucosamine/Chondroitin group (Messier et al., 2007).

Richy et al. (2003) conducted a meta-analysis that focused on studies involving the use of Glucosamine for the treatment of knee osteoarthritis. They found that high dosage and long-term supplementation provided the best result. This study did however highlight supplementation with Glucosamine alone, rather than in combination with Chondroitin:

> Our results suggests that the long-term administration of daily oral glucosamine sulphate at the minimal dose of 1500 mg during a minimal period of 3 years slows the degenerative process of the joint cartilage…[it is] counterintuitive to have patients with a long-term disorder deriving benefit from short-term interventions.

Structural Effects

Structural effects of the supplement and/or drug are characterized by the ability of the supplement or drug to retard, stop, reverse and/or prevent the progression of disease. Drugs that have a structural effect on osteoarthritis are termed Disease-Modifying Osteoarthritis Drugs

(Hunter & Hellio Le Graverand-Gastineau, 2008). Clinical effectiveness or structure modifying drugs are evaluated by the drugs' impact on joint space narrowing typically measured by radiographic imaging (Hunter & Hellio Le Graverand-Gastineau, 2008). One of the measures for progression of OA is joint space width (JSW). The grading scale utilized in most of the research, is the Kellgren-Lawrence scale. The chart below is based on some of the original research by Kellgren and Lawrence (1957):

Grade	Radiologic Features
1 Doubtful	No joint space narrowing, formation of osteophytes on joint margins
2 Minimal	Possible joint space narrowing with definite osteophytes
3 Moderate	Joint space narrowing, thinning of cartilage with sclerosis of subchondral bone
4 Severe	Marked joint space narrowing, possible bone deformation, severe sclerosis and large osteophytes

Gait studies. A second GAIT study looked at the effects of glucosamine and/or chondroitin—in comparison to a placebo group—on joint space width (JSW). Radiographic imaging was taken at baseline, 12 and 24 months. Exclusions included individuals with less than 2 mm of JSW. Subjects had to be at least 40 years old and have Grade 2 or 3 OA on Kellgren-Lawrence (K/L) scale (Sawitzke et al., 2008). There was no significant difference in JSW between treatment and placebo groups. The Glucosamine group had 0.013 mm less JSW compared with the Glucosamine/Chondroitin group which had 0.194 mm less JSW. JSW loss was greater with K/L grade 2 versus grade 3 (Sawitzke et al., 2008). Future research may require longer duration, and improved methods of measurement since it was found that JSW loss is much slower than previously recognized (Sawitzke et al., 2008).

Anterior Cruciate Ligament Transection (ACLT). The closest comparison to early onset osteoarthritis, is Anterior Cruciate Ligament Transection (ACLT) models. These studies

are animal studies that involve induced injury to the knee joint (s) of either rabbits or dogs. The injury may or may not be repaired, and then the animal is subjected to activity and/or treatment of some kind. Induced injuries to the ACL offer the opportunity to test pharmacological interventions aimed to stop or slow osteoarthritis progression (Silva et al., 2009). All studies involve double blind methodology.

Silva et al. (2009) performed an ACLT on the hind paw of rats. In this study, pain was assessed by Paw Elevation Time (PET). This was determined by how many seconds the rat's paw was elevated (non-weight bearing) in a 10 minute periods. Pain (PET) was highest between 4 and 7 days. Subjects received Glucosamine, Glucosamine/ Chondroitin or placebo and were harvested 70 days post-op. The dosages were equivalent to human doses (Silva et al., 2009). It was observed that the Glucosamine/Chondroitin group had significantly less severe cartilage damage vs placebo and Glucosamine groups. Also, there was a 44.6% reduction in pain (PET) in the Glucosamine/ Chondroitin group providing possible evidence of the supplements' analgesic effects (Silva et al., 2009).

Tiraloche et al. (2005) focused primarily on Glucosamine supplementation with an eight week study. Following ACLT, subjects (rabbits) received daily Glucosamine Hydrochloride supplementation. Macroscopically, subjects in the glucosamine group demonstrated a lower severity of articular cartilage lesions in all joint compartments vs placebo group. Specifically, 44% of the placebo group had cartilage disease in the Lateral Tibial Plateau (LTP) versus 14% of the glucosamine group when compared with controls. There was also a positive effect on proteoglycan retention in the lateral compartment (Tiraloche et al., 2005). Glucosamine supplementation did not prevent fibrillation or erosion of joint cartilage however there was an overall reduction in severity (Tiraloche et al., 2005).

Naito et al. (2010) also utilized the ACLT model, however, they focused solely on Glucosamine supplementation. Animal subjects were given Glucosamine dissolved in their water daily, and were sacrificed after 56 days. The study found that degenerative changes to the joint cartilage were substantially suppressed by the Glucosamine administration. Suppression of biomarkers for collagen degradation was observed, suggesting that Glucosamine has chondroprotective qualities by normalizing proteoglycan metabolism and enhancing collagen synthesis in cartilage (Naito et al., 2010).

Kamarul, Ab-Rahim, Tumin, Selvaratnam and Ahmad (2011) did not perform an ACLT, however, they did induce a cartilage defect to the femoral condyles of animal subjects. Once the defect was created, an Autologous Chondrocyte Implantation (ACI) was performed as a repair. Subjects were given Glucosamine and Chondroitin alone, in combination, or a placebo daily, and then sacrificed at either three or six months. The cartilage group treated with both ACI and Glucosamine/Chondroitin appeared thicker and resembled adjacent, untreated cartilage (Karamul et al., 2011). Microscopically, there was intense staining indicating strong proteoglycan and type II collagen. It was noted that quality of the repair was positively enhanced by groups that received the Glucosamine/Chondroitin combo rather than either of the supplements alone (Karamul et al., 2011).

Case study. There are limited studies involving humans that focus on structural effects. Van Blitterswijk, Van de Nes & Wuisman (2003) presented a case study involves a 56 year old male who suffered back pain for 15 years. The subject took standard doses of both Glucosamine/ Chondroitin daily for two years. In addition to daily supplementation, the patient maintained physical activity including exercises specific to the back. His initial diagnosis included L3-L4 disc degeneration and protrusion, and L4-L5 advanced disk degeneration.

Clinically the patient demonstrated increased ROM/function and decreased pain approximately six months after the initiation of treatment. MRI imaging taken at the onset, one and two years displayed 5-10% restoration of the L3-L4 disc. The L4-L5 (with advanced degeneration) showed no signs of improvement, but no further advancement of degeneration (Van Blitterwijk, Van de Nes & Wuisman, 2003). One question that the research poses is: what role did exercise play in this case study? As vertebral discs are avascular, did nutrient diffusion occur as a result of hydrostatic pressure secondary to exercise, leading to a slight increase in disc volume (Van Blitterwijk, Van de Nes & Wuisman, 2003). While this study focuses on the lumbar spine—not the knee—it is a case involving long duration supplementation with claims of significant structural effects, thus presented in this review.

Physiological effects. There are several studies that look at the effects of Glucosamine/ Chondroitin on biomarkers for the degenerative process of osteoarthritis, as well as effects on other joint structures besides cartilage. In one study, bone samples were taken from patients who were receiving a total knee replacement. The mean age of the subjects was 74 years. The samples were exposed to Glucosamine and/or Chondroitin in a petri dish for 48 hours. The Glucosamine/Chondroitin combination group exhibited reduced reabsorbing activities, or decreased chemical biomarkers that are responsible for the breakdown and remodeling of subchondral bone (Kwan Tat et al., 2007).

Another study observed the response of cartilage explant to cyclic loads. Wei and Haut (2009) hypothesized that if cartilage exposed to Glucosamine Chondroitin, in combination with low intensity repetitive loading, would boost proteoglycan (building block of connective tissue) uptake, thus making cartilage stronger and more resistant to damage secondary to overloads that cause acute injury. Bovine cartilage explants served as the samples, and were exposed to

Glucosamine Chondroitin daily, and then exposed to daily cyclic loading. Mechanical tissue load measurements were taken at 7, 14 and 21 days. In the presence of the supplement, cyclic loading of the explants significantly stimulated proteoglycan synthesis, resulting in a 65% increase compared to the control group. Also in the presence of the supplement, low intensity cyclic loading significantly decreased the cell death by ~73% after 21 days (Wei & Haut, 2009). While the study does suggest that an athlete could take the supplement in order to protect joint cartilage from moments of excessive overload, it doesn't answer whether it can mitigate the long-term effects of osteoarthritis (Wei & Haut, 2009).

Lippiello (2006) found that Glucosamine Chondroitin effectively stimulated neosynthesis of collagen in cell cultures of ligament, tendon and cartilage tissue (in humans). There was an increase in collagen synthesis in ligament cells by 69%, chondrocytes 56% and tenocytes 22%. Traditionally, Glucosamine Chondroitin has been utilized as symptomatic relief via anti-inflammatory actions, however, this study suggests that there is an advantage to such a therapy for sports related injuries as there is a possibility that the supplements enhance the natural healing/repair process and potentially minimize non-steroidal anti-inflammatory (NSAIDs) use (Lippiello, 2006).

A study involving cartilage explants from race horses, suggests both symptomatic and structural benefits from Glucosamine/Chondroitin supplementation. Orth, Peters & Hawkins (2002) found that Glucosamine inhibited prostaglandin and nitric oxide production, which are believed to have catabolic properties towards articular cartilage. Humans typically take pain-relievers such as ibuprofen for treatment of joint/muscle pain. These are known as Cox-2 inhibitors—which inhibit the release of prostaglandin which triggers inflammatory response (Orth, Peters & Hawkins, 2002). This study suggests that Glucosamine may have the same anti-

inflammatory properties as some over-the-counter pain medications. The study also found that the combination of the two supplements was shown to decrease proteoglycan degradation, which is a building block of cartilage (Orth, Peters & Hawkins, 2002).

Glucosamine and Chondroitin Use in Athletics

Studies involving young, athletic subjects are limited. Ostojic, Arsic, Prodanovic, Vukovic & Zlatanovic (2007) looked at the effects of Glucosamine on recovery following acute knee injuries. Pain and level of function were measured weekly, for four weeks of Glucosamine supplementation of 1500 mg/day. There were significant improvements in range of motion with knee flexion and extension at the end of the four weeks, but overall Glucosamine had little effect on recovery of injury. The study did only involve male subjects, and the improvements on range might be expected as a part of the normal healing timeline.

Discussion

Limitations of Research

Demographic limitations. Many of the studies focused primarily on middle to late aged individuals—osteoarthritis is typically a disease that afflicts this age group. The average age of the GAIT participants in the first study were 59 years, and already have diagnosed osteoarthritis. Another limiting factor was that participants could not have had a previous traumatic injury to the knee. Both of these factors exclude early onset OA secondary to acute injury. On the other hand, the GAIT study was the only study that really represented a broad spectrum sample including over 1,500 participants from 16 different rheumatology centers across the United States. Some of the research utilized only male or female subjects.

Longitudinal limitations. Most studies were short duration studies typically between four weeks to six months, with the exception of the case study which was three years. The GAIT trials were all six months in duration. The longitudinal studies in this review, specifically ACL injury follow-up studies, were all several years in duration, however, did not focus on Glucosamine/Chondroitin supplementation, but rather the presence of osteoarthritis following injury. Research indicates that osteoarthritis may develop within 10-20 years post injury. This would imply that most studies would need to be at least 10 years in duration, and focused on a younger subject group, to study the preventative effects of Glucosamine/Chondroitin supplementation.

ACLT limitations. The studies involving ACL transection models involve animals and have tried to closely mirror the subsequent development of osteoarthritis following ACL injury in humans, and the impacts of Glucosamine/Chondroitin supplementation have on this process. Of course animal trials are limited in that human beings may react differently than the subject animals. Another limitation of the ACLT models, is the fact that once the injury is induced, it is not always reconstructed. So the animals develop osteoarthritis, as to be expected from instability associated with injury, but in humans, most of the time an ACL tear will be reconstructed. Secondly, most of the studies are a matter of weeks whereas athletes who suffer an ACL tear in their youth will potentially be dealing with their injury over the course of a lifetime.

Cost limitations. The National Institute of Health (2008) indicates that the GAIT study cost 12.5 million dollars. This is a six month trial. A two-month's supply of Walgreens brand Glucosamine Chondroitin currently cost $28.99 (Walgreens, 2013). The costs of supplying a viable sample size with supplements over a long period of time i.e. 10 years would be

~$1800/person. This is not mentioned as a limitation in any of the studies this literature review looked at, but viewed as a potential limitation for future studies.

Bias limitations. There is a potential for bias amongst manufacturers who are making claims about the positive effects of the supplements, when the only supportive research is coming from their laboratories, conducted by their employees. Without FDA regulations similar to drug testing/trials, and with no independent research to support similar claims, it calls into question the reliability of the claims that these suppliers are making about their supplements.

With respect to studies that involve imaging such as radiographic (x-ray) or magnetic resonance (MRI), there is potential for bias and margin-of-error based on several factors: different types of machines, dispute over which type of imaging to use, variance between practitioners when measuring joint space or diagnosing severity of osteoarthritis. This may not be an issue for single site studies where these variables can be controlled, but more of an issue for multi-site studies across the country, like GAIT.

Conclusion

Research supports the notion there is a high risk of developing early onset of osteoarthritis following knee injuries. If a college athlete sustains an ACL tear at the age of 18, even with a successful reconstruction, research states that that individual could develop OA as early as age 28. Hootman and Albohm (2012) looked at the number of ACL tears and correlating costs of OA management in a lifetime. On average, there are about 75,000 ACL reconstructions each year. The cost of managing OA over the course of a lifetime is estimated at $285,000. In 2009, 679,260 knee replacements were performed secondary to knee OA, totaling more than $34 million. Based on the statistics of ACL injuries and predisposition to

osteoarthritis, there is a strong push towards prevention of ACL injuries. The first goal, prevention of injury, is typically executed with neuromuscular training programs for the lower extremities.

This literature review looked at prevention of secondary osteoarthritis following injury. Research indicated that Glucosamine and Chondroitin may be effective of maintaining the current state of articular cartilage, or helping to maintain its sponge-like qualities, as long as the OA is mild to moderate. Studies demonstrate that there are potential analgesic effects of Glucosamine, and that Chondroitin may help to reduce swelling. Structurally, Glucosamine and Chondroitin may provide increased volume to articular cartilage and vertebral discs. It has been shown to boost collagen in not only cartilage, but ligaments and tendons. Research also indicates that the two supplements may inhibit chemical biomarkers that cause breakdown of cartilage. Additionally, the effects of Glucosamine and Chondroitin may be boosted by regular exercise which allows for hydrostatic pressure or diffusion of nutrients into cartilage.

Another area of interest may be the comparison of Glucosamine and Chondroitin versus Ibuprofen or Naproxen in regards to long-term effects of consumption, the safety and/or risk associated with long-term consumption, and the cost of long-term consumption. While Glucosamine/Chondroitin is likely more expensive, it has been deemed relatively safe with minimal side effects. Non-Steroidal Anti-inflammatories (NSAIDs) like Ibuprofen or Naproxen have long been associated with gastrointestinal disorders if taken long-term and is abused. These are common medications taken for joint pain, and may have increased risk with individuals over age 60—who are commonly afflicted with conditions like osteoarthritis (Food and Drug Administration, 2009b).

Despite the research supported effects of Glucosamine and Chondroitin, less than half of 345 rheumatologists surveyed across the United States believe that Glucosamine/ Chondroitin are beneficial to their patients. Further, 60% believe that the supplements are "not very" or "not at all" beneficial (Manek et al., 2010). Of course, most rheumatologists are seeing patients with established osteoarthritis or chronic conditions like rheumatoid arthritis. This excludes the subset of young or middle aged adults who are suffering from early-onset osteoarthritis. At this time, based on the above literature review, there is limited research to support long term Glucosamine/Chondroitin supplementation and the potential effects it may have on preventing the onset and/or slowing the progression of osteoarthritis following traumatic knee injuries.

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