THE STATUS OF GLUCOSAMINE FOR THE RELIEF OF OSTEOARTHRITIS

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Abstract

Glucosamine is an amino sugar molecule used by many people to relieve the pain, discomfort, and progression of osteoarthritis. The benefit of using glucosamine to treat osteoarthritis has been supported by several clinical trials. However, it is noted not all clinical trials using glucosamine have been consistent. This article starts by discussing what osteoarthritis and glucosamine are. The article then reviews and discusses some key clinical trials in which a role for glucosamine in the treatment of osteoarthritis is tested. The article concludes with a discussion of questions that should be answered in future clinical trials.

What is Osteoarthritis and How is it Treated?

Osteoarthritis is a degradation of the joints. Age related for the most part, osteoarthritis tends to be worse in weight bearing joints. Affected joints are difficult to move, painful and can exhibit symptoms of tenderness, stiffness, effusion (swelling) and, in more severe cases, locking. Actual physical damage occurs to the articular cartilage and subcondrial bone. These two structures are anatomical components of joints and move
against each other. Limitation of joint motion due to pain or discomfort can result in further physical difficulties including muscle weakness and atrophy and weakened ligaments and tendons. Although osteoarthritis is not life threatening, it is life limiting and affects quality of life.

Multiple events cause osteoarthritis including mechanical stress, obesity, loss of muscle strength, accidents and trauma, infections, nerve damage, biochemical changes, endocrine disorders, genetics, surgery, and chronic diseases such as diabetes. Typically, normal joint function causes the compression and release of the cartilage located in the joint. Cartilage is avascular, alymphatic, and aneural. Compression of the cartilage releases aqueous liquid into the space in the joint (joint space). Fluid in the joint space exchanges with fluid from blood vessels serving the joint space. Release of the compression allows the cartilage to expand absorbing fluid back into the cartilage. The reabsorbed fluid also brings fresh nutrients picked up from the blood vessels serving the joint space. During osteoarthritis, there is an increase in the number of chondrocytes (cells that secrete the matrix of cartilage and become embedded in it) along with an increase in proteoglycans and type II collagen, two structural proteins of cartilage. There is also an increase in the synthesis of bone by osteoblasts (cells that secrete the matrix for bone
formation) that invade the joint space. Increases in the synthesis of bone appear to lead to formations of calluses, micro-fractures, and decreases in joint space resulting in joint stiffness, pain, and inflammation. In hip and knee osteoarthritis, there is a loss of movement, pain and loss of normal cartilage function. There can also be a decrease in joint stability. Increases in ossified substances in the joint can lead to joint locking.

Standard courses of treatment of osteoarthritis include physical therapy, exercise and the use of analgesics such as acetaminophen, and non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, or celecoxib. In some cases, osteoarthritis patients receive injections of corticosteroids or hyaluronic acid. In severe cases, surgery to remove material from the joint (osteotomy) or joint replacement is performed. In addition, there are many non-pharmaceutical products on the market for the treatment of osteoarthritis. Glucosamine is a non-pharmaceutical product used by patients to relieve the symptoms of osteoarthritis. This review briefly summarizes the current status of glucosamine with respect to its efficacy and safety when used to relieve the symptoms of osteoarthritis, particularly of the knee. Comment is also made regarding future research paths for glucosamine.
What is Glucosamine?

Glucosamine is an amino monosaccharide (sugar). It is synthesized by humans (and other animals) from glucose. Glucosamine is a precursor molecule in the cellular synthesis of glycosolated lipids and proteins. In humans, glucosamine, in the form of glucosamine-6-phosphate, is found in all cells and is required for the synthesis of glycosaminoglycans, proteoglycans, and glycolipids. These three classes of molecules are components of connective tissue, synovial fluid, and other tissues. When prepared for use as a supplement, glucosamine is generally in the form of glucosamine sulfate, glucosamine hydrochloride or N-acetyl-glucosamine.

Another molecule, chondroitin, or more accurately, chondroitin sulfate, is also used to treat
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osteoarthritis often in combination with glucosamine.

Chondroitin is a sulfated glycosaminoglycan, which is a chain of varying lengths of two alternating sugars. The two sugars are D-glucuronate and N-acetylglucosamine-4/6 sulfate (both molecules are also found in hyaluronic acid). Since the location of the sulfanated carbon and the chain length can vary, there is a great deal of variation in chondroitin preparations. Chondroitin sulfate is a component of healthy connective tissue. Chondroitin provides for structure and elasticity of cartilage.

Figure 2: Chemical structure of one unit in a chondroitin sulfate chain. The length of the chondroitin chain can vary. If the chondroitin sulfate chain contains chondroitin-4-sulfate, then $R_1 = H$, $R_2 = SO_3H$, and $R_3 = H$. If the chondroitin sulfate chain contains chondroitin-6-sulfate, then $R_1 = SO_3H$, $R_2 = H$, and $R_3 = H$.

Efficacy of Glucosamine in the Treatment of Osteoarthritis

Before discussing the efficacy of glucosamine for the treatment of osteoarthritis, some background in how improvement in the condition of osteoarthritis is clinically measured will be useful. The symptoms of pain, stiffness and movement associated with osteoarthritis are evaluated using patient questionnaires such as the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index or the Lesquesne Index. A
physician's examination is also used to access joint strength and mobility. Visual examination of the physical condition of the joint itself is done by radiological analysis such as X-rays. Radiological analysis provides data on the amount of joint space as well as obstructions in the joint from excess bone growth. Radiological data is quantitated using the Kellgren-Lawrence Grading Scale. It is best when data from patient questionnaires correlates with a physician's examination and with radiological analysis.

Clinical studies using glucosamine to treat osteoarthritis have been inconsistent with respect to efficacy. However, there are several clinical studies that indicate that glucosamine does appear to reduce pain and discomfort associated with osteoarthritis particularly of the knee. Several clinical trials will be reviewed and the strengths and weaknesses of these studies will be noted.

In 2001 and 2002, two long term, randomized placebo-controlled clinical trials provided evidence that glucosamine sulfate slowed the progression of osteoarthritis damage to the knee and could also decrease the symptoms (1,2). In the 2001 study, the WOMAC questionnaire was used to access pain and stiffness and radiological data was used to access the actual physical condition of the joint. Patients using glucosamine were more likely to
report reduced pain and stiffness related to osteoarthritis of the knee versus patients on
placebo. In addition, patients taking glucosamine showed reduced joint narrowing when
the knee was visualized radiologically. However, there was no obvious relationship
between the symptomatic and visual findings (1). In the 2002 study, glucosamine delayed
progression of knee osteoarthritis and the symptoms of pain and stiffness were decreased
(2).

Earlier conclusions made from clinical trials reported in 1981 (3) and 1994 (4) were
confirmed by the 2001 and 2002 reports described above. However, not all clinical trials
performed using glucosamine as a treatment for osteoarthritis have arrived at the same
conclusion. For example, the Glucosamine-Chondroitin Arthritis Intervention Trail (GAIT)
in 2006 (5) did not provide evidence that supported 100% of the conclusions drawn in the
2001 and 2002 clinical trials described in the preceding paragraph. However, the authors of
the GAIT report did suggest that their clinical data supported the idea that glucosamine in
combination with chondroitin sulfate may be effective in a subgroup of patients with
osteoarthritis of the knee and who were experiencing moderate to severe pain. Results of
this kind indicate that certain patients with osteoarthritis may benefit from treatment with
glucosamine or glucosamine and chondroitin in combination.
Clinical studies using glucosamine to relieve the symptoms of osteoarthritis are further complicated by the multiple forms of glucosamine available on the market. A report that examined this question indicated that glucosamine sulfate is the best form of glucosamine to use for the treatment of osteoarthritis (6). Yet another report indicated glucosamine sulfate and glucosamine hydrochloride are each equally safe and effective for the treatment of osteoarthritis (7). Observations of this type show the critical need for different manufacturers of glucosamine to perform their own clinical trials on their own preparations of glucosamine.

Clinical trials that compared the effectiveness of glucosamine to ibuprofen for treating the symptoms of pain associated with osteoarthritis have also been performed. Three different reports (8-10) provided data that suggested that glucosamine sulfate was as effective as ibuprofen for treating osteoarthritis particularly of the knee (8,9), but also of the tempromandibular joint (10). One of the reports (8) went a step further and provided data that suggested
that not only was glucosamine sulfate as effective as ibuprofen for osteoarthritis of the knee, but that glucosamine sulfate was better tolerated by patients than ibuprofen.

Some investigators have suggested that the combination of glucosamine with NSAIDs like ibuprofen may act synergistically since the two agents are believed to exert their effects through different mechanisms (11). In fact, it has been further suggested that the combination of glucosamine with NSAIDs may allow patients to decrease their dose of the NSAIDs (11).

Finally, some investigators have tested topical application of glucosamine for the treatment of osteoarthritis. Glucosamine in combination with chondroitin when applied topically in a cream base has been shown to decrease pain associated with osteoarthritis (12,13).
Safety of Glucosamine

Glucosamine is safe. Even though it is very widely used, there have been few reports of side effects or adverse reactions. There has been only one report of allergic reaction to glucosamine (14) and no reports of allergic reactions to those with sensitivity to shellfish (15). It is, however, suggested that those with shellfish sensitivities use glucosamine preparations from shellfish sources with caution.

There has been one report of a single patient with asthma who experienced shortness of breath when taking glucosamine (16). However it was not clear if this adverse event was actually related to the glucosamine.

A case report discusses the death of a patient taking both warfarin and glucosamine (17). Again, there was no clear relationship between the use of warfarin, glucosamine, and the death. However, it is advised that patients taking warfarin speak to their physician before taking glucosamine.

Since glucosamine is an amino monosaccharide (a sugar), there has been concern that regarding the use of glucosamine by diabetics. However, evidence available thus far
indicates that this concern appears to be unfounded (18). Regardless of this conclusion, it is best for diabetics to speak with their physician before using glucosamine.

Finally, there have been reports of gastrointestinal upset among a small number of people using glucosamine (19). The gastrointestinal upset was not serious, may not have been related to the glucosamine and seemed to be greatest in those patients who already had gastrointestinal upset before taking the glucosamine.

**Possible Mechanism of Action of Glucosamine in the Treatment of Osteoarthritis**

Although there is clinical evidence that indicates that glucosamine is beneficial to the osteoarthritis patient, an understanding of the mechanism by which glucosamine functions can increase confidence in the clinical observations and also help establish useful treatment protocols. Glucosamine is thought to improve the symptoms of osteoarthritis through a number of mechanisms. Glucosamine is believed to have anti-inflammatory properties. There is also evidence that indicates glucosamine is able to stimulate the normal metabolism of chondrocytes found in cartilage. However, a precise mechanism of action has not yet been established and further work is needed.
Conclusions

There is clinical evidence that glucosamine is effective for relieving pain and discomfort associated with osteoarthritis, particularly osteoarthritis of the knee, and therefore may be a good alternative to using acetaminophen, NSAIDs, or corticosteroids. Glucosamine is considered to be safe although it should be used with caution by those patients with a shellfish allergy, or those who have diabetes or asthma, or by those taking warfarin. Additional clinical studies to more clearly define best dosages, routes of administration, and best chemical form of the glucosamine are needed so that health care providers and patients can make well informed choices for treatment. Clinical trials designed to more clearly identify the type of patient best helped by glucosamine would also be useful. Finally, each supplier of glucosamine should perform a small clinical study to show that their particular preparation of glucosamine is effective for the treatment of corticosteroids.
References


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