Introduction

Degeneration of joint cartilage due to osteoarthritis is one of the most common musculoskeletal ailments seen in primary care and orthopaedic practices, affecting some 40 million Americans including nearly everyone over the age of 65 (1). Traditional management of the disease focuses on treating the symptomatic joint pain with acetaminophen or NSAIDs (non-steroidal, anti-inflammatory drugs). While these treatments provide pain relief, they ignore the pathophysiology of osteoarthritis and, in the case of NSAIDs, may worsen the condition by inhibiting cartilage regeneration (2). For over twenty-five years, physicians in Europe have been recommending the usage of a naturally occurring carbohydrate, glucosamine, for their osteoarthritic patients, apparently with great success. Despite the extensive European literature on the benefits of its usage, glucosamine has, until recently, been largely dismissed as a "folk-remedy" by the American medical establishment. Over the past decade, glucosamine has gradually made its way onto the shelves of health food stores in the U.S. as a dietary supplement. Personal testimonials as to the benefits of its usage have generated great popular interest and a patient-driven scientific interest in glucosamine and its actions. This paper aims to examine the beneficial effects of glucosamine on osteoarthritic patients by reviewing the current medical knowledge on the mechanisms of degenerative joint changes in osteoarthritis and the molecular basis for glucosamine's action. In addition, this paper will review a number of controlled clinical trials of glucosamine treatment in osteoarthritic patients, and compare them to similar studies utilizing traditional treatments.

Basic Joint Structure

Synovial joints consist of two major components: articular cartilage which covers the articulating ends of the bones making up the joint, and synovial fluid which fills the articular cavity between the bones. Articular cartilage functions in resisting the compressive, tensile, and shear forces that occur during normal joint movements (3). Cartilage is composed chiefly of extracellular matrix secreted by the numerous chondrocytes contained within. The extracellular matrix consists of a fibrous collagen network and a high concentration of proteoglycan aggregates. Proteoglycans are large molecules found in all connective tissue consisting of a core protein and one or more polysaccharide glycosaminoglycan chains, which are themselves composed of a sulfated amino sugar (either N-acetylglucosamine or N-acetylgalactosamine) and a uronic acid (4). The entire molecule is highly negatively charged and hydrophilic, serving to attract and maintain water molecules within the extracellular matrix (4). The high water content of the extracellular matrix allows for the diffusion of nutrients necessary to maintain the health of the chondrocytes, and provides much of the compressive strength of the articular surfaces. While the collagen component of the extracellular matrix appears to be metabolically stable, the proteoglycan constituents undergo a turnover process in which catabolic cleavage and removal of old molecules are in balance with the synthesis and deposition of new ones (3). The highly viscous synovial fluid has both shock-absorbing and lubricating properties within the joint cavity (5). The major organic constituent of synovial fluid is hyaluronic acid (5), a glycosaminoglycan consisting of a long chain of N-acetylglucosamine and glucuronic acid repeats (4).

Joint Degeneration in Osteoarthritis

Osteoarthritis is characterized by macroscopic and molecular changes in the cartilage and synovial fluid of the joints. Typical osteoarthritic findings include a degeneration of joint cartilage (1) and an increase in volume and decrease in viscosity of synovial fluid (5). Cartilage degeneration results from a perturbation in the metabolic turnover of proteoglycans, causing catabolism to dominate over production (3,6). In addition, proteoglycans synthesized during the course of the disease often show changes in chain length and sulfation when compared to normal, causing those proteoglycans that are synthesized to have altered function (3). Osteoarthritic changes in the synthesis pathway of hyaluronic acid result in a reduction of both its concentration and molecular weight, causing the decrease in synovial fluid viscosity (5). The decreased lubricating and shock-absorbing capabilities of the diseased joint permit the rubbing of joint surfaces against each other. This results in pain, decreased mobility, and inflammation of the joint. This inflammation causes the increase in synovial fluid volume seen in osteoarthritis.

The Molecular Role of Glucosamine

It has been known since the early 1950s that the addition of exogenous glucosamine to cartilage cells in vitro results is substantially increased production of glycosaminoglycans (6). In the glycosaminoglycan biosynthetic pathway, fructose-6-phosphate is aminated in the presence of glutamine, yielding glucosamine-6-phosphate. This is then acetylated and added to the growing glycosaminoglycan chain. Glucosamine per se is not an intermediate in this pathway. However, radiolabeled glucosamine has been shown to be readily incorporated into glycosaminoglycans in vitro (7). If glucosamine is not an intermediate in the synthetic pathway, how can we explain its direct and efficient incorporation into glycosaminoglycans? Evidently, exogenous glucosamine is a good substrate for a kinase that converts it into glucosamine-6-phosphate, the rate-limiting intermediate in the glycosaminoglycan synthetic pathway (6). Thus, exogenous glucosamine provides raw material for the production of glycosaminoglycans and proteoglycans (including hyaluronic acid), bypassing the rate-limiting step of the standard biosynthetic pathway. Recent studies (8) have suggested that hyaluronic acid suppresses the accelerated rate of cartilage catabolism in osteoarthritis. Therefore, at least in animal tissue models, glucosamine supplementation appears to increase the synthesis and decrease the catabolism of glycosaminoglycans, countering the effects of osteoarthritis. Additionally, there appears to be a regulatory link between glycosaminoglycan and collagen syntheses, such that increased production of one results in increased production of the other (6). An increase in collagen therefore accompanies the increased glycosaminoglycan synthesis seen with glucosamine supplementation, potentially aiding the repair of damaged cartilage tissue.

Clinical Trials

The clinical evaluation of glucosamine as a treatment for osteoarthritis began nearly thirty years ago when a group of German physicians administered daily injections of 400 mg of glucosamine sulfate intramuscularly, intravenously, or intra-articularly. Their patients reported a substantial reduction in pain often accompanied by increased mobility in the affected joint. However, since these were uncontrolled studies, the results were not considered definitive (6). A number of clinical trials involving oral administration of glucosamine sulfate appeared in the early 1980s, including an extensive multi-center trial in Portugal (9). In this study, osteoarthritic patients received 500 mg of glucosamine sulfate three times per day. Results of the study indicated that pain decreased steadily throughout the treatment, and ninety-five percent of the patients reported a "sufficient" or "good" clinical response. Eighty-six percent of the patients in this study reported no side effects, and those that did mostly complained of mild intestinal discomfort. A review of several early double-blind trials in Europe and the Philippines (6) indicate uniform results. Glucosamine therapy was associated with a reduction in joint pain and swelling and an improvement in range of motion. These benefits were significantly greater than placebo and were not accompanied by any reported side effects. A 1994 multi-center, randomized and controlled double-blind study (10) again examined the effects of intramuscular injections of glucosamine sulfate, this time only twice weekly. The results mirrored those of earlier studies in that patients showed a significant reduction in pain and increase in mobility. Recent studies (4,11) examining the effects of combined glucosamine and chondroitin sulfate (a glycosaminoglycan common in cartilage) treatments for osteoarthritic patients have concluded with similar results.

How Does Glucosamine Compare with Traditional Treatments

Since the 1950s, the standard treatment for osteoarthritis has been the administration of acetaminophen or NSAIDs. Acetaminophen, an analgesic, worked well to mask the pain associated with osteoarthritis, but ignored the etiology of the disease. Similarly, NSAIDs treat the symptoms of the disease (pain and inflammation) but ignore the mechanisms responsible for its development. Recently, evidence has arisen that NSAIDs may in fact directly inhibit cartilage regeneration, aggravating the disease they are meant to treat (2). Also, the negative effects of long-term NSAID use on the gastrointestinal tract have been well known for years. Clinical trials have been conducted directly comparing glucosamine therapy to standard NSAID treatment for osteoarthritis (12,13). Results indicated that pain relief was more rapid with NSAIDs, but was eventually significantly greater with glucosamine, and glucosamine had much greater tolerability by the study patients.

Conclusion

For decades, European physicians and scientists have shown a marked interest in glucosamine and its ability to benefit osteoarthritic patients. Animal tissue culture studies have demonstrated that exogenous glucosamine has the ability to bypass the rate-limiting step in glycosaminoglycan synthesis, increasing the concentration of proteoglycans in the extracellular matrix of cartilage and the synovial fluid. This, in turn, increases the water-retaining properties of these tissues, improving their lubricating and shock-absorbing functions. Additionally, since proteoglycan synthesis and collagen synthesis appear to be linked, glucosamine may stimulate the repair of damaged cartilage by increasing collagen deposition. These effects appear (at least in animal models) to demonstrate the ability of exogenous glucosamine to counter the degenerative changes seen in osteoarthritis. European clinical trials have unanimously shown the efficacy of glucosamine administration to sufferers of osteoarthritis. Every study has shown positive results with decreases in pain and inflammation and increases in mobility being common. No significant side effects have been demonstrated with regular use of glucosamine. Despite such overwhelming evidence for the benefits of glucosamine, American doctors have, until very recently, ignored it as a potential treatment for osteoarthritis. As glucosamine has become readily available in health food stores in recent years, news about its benefits have spread rapidly through the patient population. This great popular interest, and a general increased openness to alternative therapies, has given birth to scientific interest in glucosamine in the United States. Recent studies have agreed with the results of earlier trials, demonstrating the benefits of glucosamine in osteoarthritis. However, many physicians continue to adhere to the traditional therapy of analgesics and NSAIDs, despite studies on the negative effects of NSAIDs on cartilage and the gastrointestinal tract, and direct comparison studies showing an equal or increased benefit of glucosamine over NSAIDs.

In conclusion, it is clear that glucosamine can provide a clear therapeutic benefit in osteoarthritis with minimal, if any, side effects. It is likely that these effects are mediated by increased efficiency of proteoglycan synthesis. These points challenge the rationale of traditional therapy with anti-inflammatory agents. It is important for anyone considering glucosamine therapy for their osteoarthritis to consult with their physician so they may recommend the proper dosage and rule out any potential complications.

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