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VIEW POINT

THE ROLE OF GLUCOSEAMINE SULFATE ON OSTEOARTHRITIS: AN UPDATE

MD. RASHIDUL HASAN[1], H.A.M. NAZMUL AHASAN[2], MD. FAIZUL ISLAM CHOWDHURY[3], M MATIUR RAHMAN[4]

Introduction:

Osteoarthritis, the most common form of arthritis is an age related degenerative disease of joint cartilage. It is a major cause of disability and is among the most frequent form of musculoskeletal disorder. About 40 million American has been reported to be affected by osteoarthritis. Of these 80% individual are over 50 years with twice as frequent in women as in male. At least 20 million adults suffer at any one time. So huge amount of financial loss due to actual cost of therapy as well as loss of productivity in the work place. The traditional approach to manage this problem is to use symptom modifying agents like NSAID along with physiotherapy and life style adjustment. But this fails to modify the underlying degenerative process. Moreover, there are numerous adverse effect associated with NSAID that may limit their use. Some NSAID also inhibit the synthesis of glycoseaminoglycans (GAGs) and impair the body's ability to heal itself. ManKin et al showed that there is significant decrease in glucoseamine content of osteoarthritic cartilage. As there is continued wear and tear of normal cartilage and age related decline in glucoseamine synthesis in the body supplement of glucoseamine may be helpful to compensate the normal metabolic turnover of the extracellular matrix and to prevent the degradation of cartilage by stimulating the healing process when it is damaged. So the search for alternative pharmacotherapies that might influence the disease process but have fewer adverse effect has lead to trial with glucose amine sulfate alone or in combination with chondroitin. It has been suggested that glucose amine could be beneficial in promoting the regeneration of damaged cartilage from injury. In animal cartilage culture studies, glucoseamine was partially able to reverse the effects of some NSAIDs on inhibiting GAGs and collagen synthesis.[1]

How does glucose amine work?

Glucose amine is an amino monosaccharide normally synthesized in the body by chondrocytes and used to make glycoseaminoglycans (GAGs) and proteoglycans (PGs), the essential component of ground substance of the connective tissue. Exogenous glucose amine from dietary (aristle) or supplemental source can also be utilized by the chondrocytes to synthesize GAGs and PGs. Of the absorbed glucose amine, 25% will be excreted in urine, 65% excreted as exhaled CO_2 and only 10% is retained in tissues. Once it is taken up by the chondrocytes it act as a raw material for GAGs and PGs synthesis. The proteoglycans bind cations and water to form a viscous, elastic matrix that helps to lubricate the joints where cartilage is present. When the cartilaginous layer is compromised due to decreased synthesis or increased degradation, the loss of cushioning with resultant articular damage. So some scientist believe that glucose amine is the most important and rate limiting substance for the synthesis of healthy cartilage.

Chondroitin sulfate is also present in higher concentration in cartilage that provides its resiliency. For this chondroprotective activity, chondroitin is also being used along with glucose amine as therapy for osteoarthritis. [2,3]

Glucose amine has numerous effects on the health of cartilage and connective tissue sythesis in the body. When supplemental glucose amine is available to chondrocytes, they produce connective tissue faster because they can skip three chemical reactions, only needing a phosphorylation to make glucose amine-6-phosphate. Glucose amine sulfate is also required for the synthesis of hyaluronic acid (HA) by the synovial membrane. HA increase the viscocity of synovial fluid and thus serves to reduce the wear and tear stress on the articular cartilage and related joint structures. Thus glucoseamine may be helpful

1. Assistant Professor, Department of Physical Medicine, Dhaka Medical College
2. Professor of Medicine, Dhaka Medical College
3. Associate Professor, Department of Medicine, Dhaka Medical College
4. Assistant Professor, Department of Medicine, Sir Salimullah Medical College

in preventing, reversing or stabilizing the osteoarthritis.[4,5]

Glucose amine also appears to inhibit lysosomal enzymes including collagenase and phosphorylase $A_{2,}$ utilized for cartilage catabolism.[6] This gives antinflammatory properties to glucoseamine without disturbing the prostaglandin biochemistry (e.i synthesis of PG). But majority adverse events of NSAID is due to inhibition of prostaglandin synthesis. In animal studies, glucose amine blocks the generation of intrarticular superoxide radicals.[7] Glucose amine sulfate also delivers the mineral sulfur to the joint cartilage. Sulfur stabilize the connective tissue matrix of cartilage, tendon and ligament. Sulfur also alleviate arthritic symptoms due to its antiinflammatory effect.

Debate:

All most all of the studies done on oral glucose amine have used glucose amine sulfate stabilized with NaCl salt. It supplies both glucose amine and sulfur to chondrocytes. But other form of glucose amine (Nacetyl-glucoseamine and glucoseanime hydrochloride) not providing the sulfur.[8] Proponents of glucose amine hydrochloride feel that the sulfur portion of glucose amine sulfate is removed during digestion and not utilized by cartilage.[9] But the proponents of glucoseaminesulfate disagree and feel that it supplies sulfur to the chondrocytes for synthesis of kertansulfate and chondroitinsulfate (GAGs).[10] On the other hand, evidence for the use of chondroitin appears to be less than glucose amine. Some experts in this area concluded that adding chondroitin to glucose amine administration has not been shown to further improve the benefits available from glucose amine alone and it imposes additional cost with no added benefit.

How ever the preparation of glucose amine tablet varies from country to country and different pharmaceuticals products. Some 500 mg glucoseamine sulfate tablet contain 20% sulfate and 20% sodium leaving only 300 mg of elemental glucose amine. Patients taking 3 tablets getting only 900 mg per day ei. inadequate dose.[11]

Clinical studies with glucose amine sulfate.

There has been very little US research on glucose amine but in Europe, more than 300 investigation including 20 double-blind studies have been carried out on glucoseamine in the early 1980s.[8,11]

A large number of clinical and experimental investigations to determine if oral glucoseaminesulfate supplementation can compensate for age-related decline in glucoseamine synthesis and thereby block the progression of osteoarthritis and/or reverse or repair any existing joint cartilage damage.[12,13] In a recent review, the researchers indicated that glucoseamine supplementation has been shown to be effective in the treatment of osteoarthritis.[14]

Most of the original research on glucoseamine was carried out in Europe and Asia and demonstrated impressive results. Some researchers in North America have criticised the research methodology of some of these trials and suggested their own trial before glucose amine can be recommended as a treatment for osteoarthritis.[15] In 1999 and 2001 Register et al published their findings of a large randomized controlled analysis that was placebo-controlled, double blind and prospective in nature. It involved 212 patients with knee OA. Weight-bearing and anteroposterior radiographs of each knee were done at 1 and 3 years. Joint space width was also measured. Symptoms and functional status were scored every 4 months using Western Ontario and Mc Master University Osteoarthritis Index (WOMAC). The two groups had comparable base line status, but after 3 years there was no further joint space narrowing in the glucose amine group. The placebo group had further joint space narrowing and objective evidence of disease progression. Further, symptoms worsend in the placebo group over the three years period but marked reduction in symptoms of OA were observed in other group. Patients in the glucoseamine group did not experience any untoward side effects.[16,17] In the Lancet editorial it is stated that, it is time (for medical doctors) to accommodate the possibility that many nutritional products may have valuable therapeutic effects and to regain the credibility of the public at large.[18] Further more in osteoarthritis, the joint capsule becomes thickened and the synovial fluid has a reduced concentration of lactate and glucose inhibiting the synthesis of hyaluronic acid (HA). As glucose amine takes part in the synthesis of both CS and HA, and because these two compounds are depleted in OA, it has been suggested that replacing glucoseamine could be of benefit to patients suffering from OA. Bassleer et al working with human articular chondrocyte cultures showed that not only

does exogenous glucoseamine become incorporated in to mucopolysaccharides but it also appears to activate core protein synthesis in human chondrocytes. But investigations though positive, suffer from limitations of applying invitro results on human. All the variation in these studies mean that it is difficult to come to a firm conclusion as to the overall effectiveness of using glucoseamine for the treatment of osteoarthritis.

Side Effects (Adverse effect):

Although there has not been a systematic evaluation of the adverse effects associated with supplemental glucoseamine sulfate, a few studies have made mention of observed adverse effects in their individual studies, despite the small number of patients. Short term adverse effects are mild and infrequent. These are constipation, nausea, heart burn, anorexia. Less commonly observed side effects were palpitation, skin reaction and painful heavy legs.[19-21] Recently, concern regarding the ability of glucoseamine to adversely affect glucose tolerance has been voiced.[22] How ever many studies in humans have failed to demonstrate a significant effect on blood glucose at oral therapeutic dose. Pronounced glucose intolerance has not been demonstrated in the many well-documented studies.[23-27] Thus glucoseaminesulfate supplementation is not an absolute contraindication in diabetic and pre diabetic patients.

Drug Interaction:

Glucoseamine sulfate has no potential for interactions with any other drugs as it does not bind to plasma protein and it is not metabolized via cytochrome P450 enzyme system. Steroidal or NSAID can be administered together with Glucoseamine sulfate.[28]

Dosage:

For the treatment of OA, the usual daily dosage of glucoseamine sulfate is 1500mg per day which can be taken all at one time or in divided doses of 500 mg per dose. Individuals taking diuretic drugs may require an additional 500mg per day to compensate for the increased excretion rate with urine. Individuals weighing>200 pounds may also be advised to up their dosage to 2000 mg per day.[5,17,29] Clinical studies have shown that "Bridge Therapy" is an effective treatment regimen where by glucoseamine sulfate is administered together with NSAID at the beginning of the therapy, for approximately 2 weeks to allow GA to start its symptom modifying effect. Then NSAID is withdrawn to prevent its side effects (GIT, Renal, Hepatic)[30] Glucose amine sulfate relieves the symptoms of OA within 2 weeks and its effect persists al least up to 8 weeks.[28]

Conclusion:

In early stage of disease or injury, these factors may have a catabolic effect on the proteoglycans degradation and synthesis balance. Glucoseamine can stimulate biosynthesis of proteoglycans and restore the catabolic-anabolic balance. Some research also indicates that glucose amine may have little, if any, effect on severe cartilage injuries or advance diseases. In conclusion as osteoarthritis is a chronic condition, there is no hard evidence that supplemental glucoseamine will provide a long term cure. Most importantly, there is no enough evidence that it is safe to take the compound for an extended period. So the need for long term clinical trials has been emphasized.[31,32] Thus glucose amine should be used judiciously for limited period of time, say for no more than 3 months at a time.[33] But the fact is glucose amine sulfate takes 2 weeks to start its symptom relieving effect and its lasts only to up to 8 weeks. It may be due to mineral sulfur for its anti-inflammatory effect. Long term cure needs its use for extended time through its disease modifying effect (if at all). Glucose amine may have its place in the athletic world as young athletes are in a never ending state of collagenous tissues damage and repair, making them primary candidates for OA in their later years (much earlier than normal individual). Glucose amine supplement may speed up the recovery process by aiding in the repair of the damaged tissues and thus slow down the progress of degenerative change of articular cartilage.

References:

1. Buccl L. Nutrition applied to injury rehabilitation and sports medicine. CRC Press, 19 May, 1977.
2. Williams & Wilkins. In: Basic medical Biochemistry: A Clinical Approach. 1996: 452-53.
3. Kelly GS. The role of Glucose amine sulphate and chondroitin sulfate in the treatment of degenerative joint disease. Altern Med Rev 1998; 2: 27-29.
4. Gottlieb Marcs. Conservative management of spinal osteoarthritis with glucose amine sulfate and

chiropractic treatment. Journal of manipulative and physiological therapeutics, 1997; 20(6).

5. Lequesne et al. Journal of Rhenmatology, 1994; 21 65-73.
6. Setnikar et al, Antireactive properties of glucose amine sulphate. Arznemittel Forschung, 1991; 41: 157-101.
7. Murray, Michael, T. Glucose amine sulphate: Nature's Arthritis Cure. Excerpt from The chiropractic Journal, March 1998.
8. Bucci LR. Nutrition Applied to Rehabilitation in sports medicine. CRC Press, 1995.
9. Murrary MT, Glucose sulfate: effective osteoarthritis treatment. American Journal of Natural Medicine, September 1994; 1: 1.
10. Murray MT. Which is better, glucose amine sulfate or chondroitinsulfate? American Journal of Natural Medicine, 1997; 4: 6-8.
11. Glucose amine sulfate. Altern Med Rev. 1999; 4: 193-5.
12. Vidal,Y. and Plana,R.R., et al. Articular Cartilage Pharmecology. In vitro studies on glucose amine and NSAIDs. Pharmacol Res Comm 1978; 10: 557-569.
13. Deal, C.L., Moskowitz, R.W. Nutraceuticals as therapeutic agents in osteoarthritis. The role of glucose amine, chondroitin sulfate and collagen hydrolysate. Rheum Disc Clin North Am 1000; 25 (2) 379-95.
14. Barclay, T.S., Tsourounis, C., Mc Cart, G.M. Glucose amine. Ann Pharmacothrer 1998; 32 (5): 574-9.
15. Reginster, Y.J., Deroisy, R., Paul, I., et al. Glucose amine sulfate significantly reduces the progression of knee OA over 3 years: a large randomized, placebocontrolled, double-blind prospective trial. Arthritis Rheum. 1999; 42 (Suppl)
16. Reginster, Y.J et al. Long term effect of glucose amine sulfate on OA progression: a randomized, placebo controlled clinical trial. Lancet 2001; 27; 251-6.
17. Mc Alindon, T., Glucose amine for OA: dawn of a newera? Lancet 2001; 357: 247-248.
18. Mc. Carty, Mark F. Glucose amine for Wound Healing. Medical Hypotheses 1996; 47: 273-275.
19. Drovanti A., BienaminiAA., Rovati AL: Therapeutic activity of oral glucose amine sulfate in OA a placebo-controlled double blind investigation. Clin Ther 1980; 3: 260-272.
20. Vajranetra P. Clinical trial of glucoseamine compounds for OA of knee joints. J Med Assoc Thar 1984; 67: 409-418.
21. Adams ME, Hype about glucose amine. Lancet 1999; 354: 353-354.
22. Monauni, T., Zenti, M.G., Cretti, A., et al. Effects of glucoseamine infusion on insulin secretion and insulin action in human Diabetes 2000; 49: 926-35.
23. Noak W, Fisher M. Forster KK, Rovati LC, Setnikar I, Glucose amine sulfate in OA of the knee. Osteoarthritis cart 1994; 2: 51-59.
24. Mc Clain DA, Crook ED. Hexoseamines and insulin resistance. Diabetes 45: 1003-1009, 1996.
25. Muller-Fassbender, H. et al. glucoseamine sulfate compared to ibu profen in OA of the knee. Osteoarthritis cartilage 1994; 2: 61-69.
26. Ac Aliudon, T.E., Lavelley, M.P., Guilin, J.P., Felson, D.T. Glucose amine and chondroitin for the treatment of OA: a systematic quality assessment and meta-analysis. JAMA 2000; 283: 1469-75.
27. DONA MONGRAPH September 2000 Drug interactions, P-49.
28. Mlurray, Michael, T. glucoseamine sulfate: nature's arthritis cure. Excerpt from The chiropractic Journal- March 1998.
29. Rovati LC: The clinical profile of glucoseamine sulfate as a selective symptom modifying drug in OA: Current data and perspectives. Osteoarthritis Cartilage 1997; 5: (Suppl.A): 72.
30. Harvard Health; Effectiveness of glucose anime depends on the degree of injury or arthritis. Letter 25 (8), 3 June 2000. (Health: 64@ Yahoo.com)
31. Towheed TE, Anastassiades TP. Glucose amine and Chondriotin for treating symptoms of osteoarthritis: evidence is widely touted but incomplete. JAMA 2000; 283: 1483-84.
32. Adams ME: Hype about glucose amine. Lancet 1999; 354: 353-54.
33. Kayne, S.B. et al: Is glucose amine an effective treatment for osteoarthritis? A meta-analysis: The Pharmaceutical Journal 2000; 265: 7123, P759-763.