Assistant Personal Work

The Role of Glucosamine Sulfate in Osteoarthritis

written by

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I. Preface

My interest in glucosamine sulfate arose during the time at the college in Canada. At this point in time, relatives of mine asked me for a remedy against pain caused by degenerative joints. Not knowing much about osteoarthritic pain I started a search for the „cure“ of it. While reading articles and books about this subject I tumbled over a remedy called glucosamine sulfate. Readily avaiable in stores in North America I started to send some packages back home. After I while those relatives informed me that their pain has disappeared or at least got better.

When choosing a subject for the critical literature reading course at the Swiss Chiropractic Institute I did not have to go a long way before I decided to do my literature review about the role of glucosamine sulfate in osteoarthritis.

The Role of Glucosamine Sulfate in Osteoarthritis

II. Introduction

Osteoarthritis (OA) is a noninflammatory degenerative joint disease marked by degeneration of the articular cartilage, hypertrophy of bone at the margins, and changes in the synovial membrane, accompanied by pain and stiffness (14). It is estimated that OA of the hands affects more than 42 million (32.5%) Americans aged 25-74 and this prevalence is expected to rise further as the population ages (15). Although it is one of the most common forms of rheumatic diseases, the precise biochemical cause of OA remains unknown. What is known, however, is that the disease process is characterized by a predominance of degradation vs. repair of cartilage proteoglycans and of subchondral bone. This ultimately leads to a functional deterioration of the joint, which typically results in the painful features observed in patients with OA. Additional symptoms such as stiffness, joint swelling, deformity, and crepitus also develop with continued turnover of cartilage matrix. The development of variable degrees of inflammation (e.g.synovitis) in the joints of these patients occurs secondary to the increased release of various inflammatory mediators, including metalloproteinases (e.g. collagenase, gelatinase, stromelysin) and chondrocytes.

Risk factors have been identified that may predispose patients to the development of the disease. These are age, gender, race, genetic predisposition, obesity, mechanical stress, joint trauma, congenital and developmental bone and joint disorders, prior inflammatory joint disease and endocrine and metabolic diseases. Epidemiologic data show that age is considered a major determinant of OA, with higher incidence rates reported in patients with increased age (15).

Most current treatment modalities of OA are targeted at primary and secondary prevention. Primary prevention strategies include patient education, protecting the joint from further injury, exercise and weight reduction, and avoidance of excessive repetitive motion. Secondary prevention is primarily palliative and involves both nonpharmacologic and pharmacologic therapies, as well as surgery. Nonpharmacologic treatment approaches include exercise rehabilitation; physical and occupational therapy; appropriate use of braces, bandages, canes, crutches, and walkers; and the application of heat or cold therapy. The main goal of pharmacologic management is to minimize the painful symptoms. Although the American College of Rheumatology guidelines for therapy of OA recommended acetaminophen as a first-line option (4), there are many other effective topical and oral agents available to treat patients with OA. These include agents such as capsaicin, methylsalicylate, nonsteroidal antiinflammatory drugs (NSAIDs), and when indicated, opiates and corticosteroids.

Non-Pharmological
- Patient education
- Programmed exercises
- Weight loss
- Joint protection
- Thermal modalities

Pharmacologic Therapy
- Nonopioid analgesics

Topical analgesics
NSAIDs
Intra-articular steroids
Intra-articular hyaluronate
Opioid analgesics
Surgical Approaches
Arthroscopic débriment
Osteotomy
Total joint arthroplasty

Table 1: Current treatment of OA

Unfortunately, none of these drugs can control the evolution of OA and some have been implicated in accelerating its progression. To date, there is no evidence that NSAID treatment favorably modifies the progression of joint breakdown in humans with OA, in fact, several, but not all, NSAIDs inhibit the synthesis of proteoglycans by cartilage in vitro in a concentration-dependent fashion, and some have been shown to accelerate progression of cartilage degeneration in vivo in animal models of OA (4,13). Because of the possible serious adverse events associated with the long-term use of some of the aforementioned medications, recent experimental efforts have been directed at identifying „chondroprotective" agents that may repair, or at the very least, slow the degradation of articular cartilage in OA. It has been suggested recently that the preferable label is Disease-Modifying OA Drug (DMOAD) (13). A number of these chondroprotective or DMOAD are under investigation to determine their role in joint repair and/or preservation of joint structure and function. Heparinoids, hyaluronic acid, piroxicam, tetracyclines, corticosteroids, chondroitin, and glucosainine sulfate are among the various agents that have been described as possessing chondroprotective properties (3,13). Recent clinical experience with one of these chondroprotective agents, namely, glucosamine sulfate, has resulted in controversy over its use as an alternative agent for the treatment of OA.

Glucosamine sulfate

Glucosamine, an amino derivative of glucose, occuring in many polysaccarides (14), is an intermediate substrate used in the synthesis of glycosaminoglycan and proteoglycans by articular cartilage. It is present as a natural compound in almost all human tissue and has a special tropism for cartilaginous tissue, where it is readily incorporated into proteoglycan molecules.

Glucosamine sulfate, which has a relatively low molecular weight (456.42), is the sulfate salt of the natural aminomonosaccharide, glucosamine. Glucosamine itself has a molecular weight of 179.17. More than 50% of glucosamine is nonionized at the pH of the small intestine, allowing rapid absorption. At a pH of 7.4, 75% is in the nonionized form. Following oral administration of glucosamine sulfate, at least 90% is absorbed, with 10% appearing in the feces. Approximately 20% to 30% subsequently appears in the urine, and up to 70% appears as exhaled CO_2 with approximately 8% to 12% retained in the tissues. In studies in rats, autoradiographs demonstrate the appearance of C^{14}-labeled glucosamine in cartilage 4 hours after ingestion.

The pharmacokinetics of glucosamine sulfate have been investigated in humans, dogs and rats. After intravenous administration of C^{14} – labeled glucaosamine sulfate in dogs, the half-life of radioactivity in the plasma is 0.28 hour. After 1 to 2 hours, all radioactivity has disappeared from the plasma and now appears incorporated in plasma proteins. The pharmacokinetics after oral administration are similar to those after intravenous administration, but concentrations are five times lower.

In addition to the effect of glucosamine on cartilage metabolism by stimulating chondrocytes to produce glycosaminoglycans and collagen (4), which has only been described in vitro, anti-inflammatory effects have been described. In rat models of inflammation glucosamine has demonstrated anti-inflammatory activity. Although this effect is 50 to 300 times lower than that of indomethacin, the toxicity of indomethacin is 1000 to 4000 times greater, and the therapeutic margin favors glucosamine. The antiinflammatory activity of glucosamine appears related to mechanisms that are substantially different from those of NSAIDS, which act primarily through inhibition of cyclooxygenases. Glucosamine is ineffective as an inhibitor of cyclooxygenase and thus its effects are prostaglandin independent.

In North America, glucosamine is available in pharmacies and health food stores as the sulfate, hydrochloride, N-acetyl or chlorhydrate salt, and as a dextrorotatory isomer. Most clinical studies have been conducted with glucosamine sulfate; less information is available on the clinical effects of other forms of glucosamine. The sulfate and hydrochloride forms of glucosamine differ in their purity, sodium content, bioactive glucosamine, and equivalent dosages.

The most common addverse effect experinced by a small number of patients taking glucosamine sulfate is gastrointestinal discomfort (epigastric pain, heartburn, diarrhea, nausea, vomiting and dyspepsia).

III. Methodes

Pertinent citations were identified via a Medline search (1995-2000). Only literature in English language involving human subjects, all age groups and both gender, all journals and publication types were selected for review. The search was carried out using the following query terms:

- Glucosamine sulfate
- Osteoarthritis

This first search was concluded with 36 citations found. The following articles were classified as useful for this project by the author: (1,2,3,4,5,6,13).

Reviewing the reference lists of those articles led to the following additional articles: (7,8,9,10,11,12). From this total selection only original research papers were considered for the final analysis. All other papers were excluded. The articles written by Noack, Reichelt and Qiu (6,8,9) were left and used for the analysis.

A checklist tailered to the topic was then devised for the purpose of analysing the original research papers.
The checklist includes the following points:

- What kind of **study design** was used?
- Has there been a **study goal** defined?
- Has the **source of a homogeneous study group** been explained?
- Was the **number of subjects** mentioned?
- Were the **inclusion criteria** defined?
- Were the **exclusion criteria** defined?
- Was there a **comparability of the complaints?**
- What kind of **pre-treatment diagnostics** have been used?
- What was the treatment of the **treatment group?**
- How was the **control group** treated?
- What has been **the method of statistical analysis?**
- Has a **randomization** taken place?
- Was the study **double-blinded**?
- Was the **treatment described**?
- Was the **reference treatment** explained?
- Has there been a **comparison with an established treatment**?
- Was there a **comparison with a placebo** treatment?
- Any **contamination** of the study thru other medical treatment?
- How many **drop-outs** during the study?
- How was the **outcome measurement** been carried out?
- **Duration of the study**?
- **Duration of the follow up**?
- What is the **conclusion** of the author?

Finally, the selected RCTs were analysed with this checklist for methodological adequacy and scientific plausibility.

IV. Results

Checklist I: Glucosamine sulfate in osteoarthritis of the knee.
by Noack W, et al.

1. Study type	Multicenter, randomized, placebo-controlled, double-blind, parallel group design.
2. Study goal	Defining the activity and safety of GS on the symptoms of patients with OA.
3. Source of homogeneous study subjects	Patients with knee OA over 18 years of age
4. Number of subjects	252 patients of both sexes
5. Inclusion criteria	Clinical and radiological, others
6. Exclusion criteria	Radiological, medication, others
7. Comparability of complaints	Yes
8. Pre-treatment diagnostics	Yes
9. Treatment group	Sugar-coated tablets of 250mg GS each for 4 weeks, at meals, three times per day (1500mg per day of GS)
10. Control group	Placebo consited of indistinguishable tablets containing only excipients.
11. Method of statistical analysis	Fisher's two-tailed Exact Probability test Student's t-test, chi-squared and McNemar Shift test.
12. Randomization	By means of computer software in blocks of four for series of 28 pateints in each center.
13. Double blinding	Yes
14. Treatment described	Yes
15. Referrence treatment described	Yes
16. Comparison with established treatment	No
17. Comparison with placebo	Yes

18. Contamination	No
19. Drop-outs	GS: six patients; placebo: five patients
20. Measurement of outcome:	Same as inclusion
21. Duration of study	4 weeks
22. Duration of follow up	No follow up
23. Conclusion	GS may be a safe and effective symptomatic Slow Acting Drug for OA.

Most important points:

- Short study period
- No follow-up period
- No comparison with established treatment
- Methodological design of this study is well made

➢ Nevertheless, this was the best study which was analysed

Checklist II: Efficacy and Safety of Intramuscular Glucosamine Sulfate in Osteoarthritis of the Knee.
by Reichelt A., et al.

1.Study type	Multicentre, randomised, placebo-controlled, double-blind, parallel-group sudy.
2. Study goal	assessing the efficacy and safety of GS intramuscularly given on the same parameters.
3. Source of homogeneous study subjects	Not mentioned
4. Number of subjects	155 of both sexes and aged over 18 years
5. Inclusion criteria	knee OA (Lequesne's criteria), radiological stage between I and III, Lequesne's severity index of at least 4 points and symptoms of at least 6 month.
6. Exclusion criteria	Mentioned
7. Comparability of complaints	Yes
8. Pre-treatment diagnostics	Radiographs, Lequesne's index
9. Treatment group	400mg intramuscularly twice a week for six weeks.
10. Control group	0.9% saline solution
11. Method of statistical analysis	Fisher's two-tailed Exact Probability test, Student's t-test, Chi-Square test, McNemar Shift analysis
12. Randomization	Yes
13. Double blinding	Yes
14. Treatment described	Yes

15. Referrence treatment described	Yes
16. Comparison with established treatment	No
17. Comparison with placebo	Yes
18. Contamination	No
19. Drop-outs	GS: 6 patients, placebo: 7 patients
20. Measurement of outcome:	Same as enrollment criteria, but without radiographs and with a final overall judgment by an investigator.
21. Duration of study	6 weeks
22. Duration of follow up	2 weeks
23. Conclusion	The results of this study with intramuscular GS confirm the positive effects obtained with the oral preparation of the drug on pain relief and functional improvement.

Most important points:

- Similar study to the one done by Noack W.
- Short study and follow-up period
- Otherwise a methodological useful design
- No words lost about homogenous study group
- Not compared with established treatment

➢ Second best study based on my checklist

Checklist III: Efficacy and safety of glucosamine sulfate versus ibuprofen in patients with knee osteoarthritis
by Qiu GX.

1. Study type	Double-blind randomized control trial
2. Study goal	Assessment of the effcacy and safety of GS oral administered in Chinese patients suffering from OA of the knee compared to ibuprofen (ibu).
3. Source of homogeneous study subjects	178 Chinese patients with knee pain
4. Number of subjects	38 male and 140 female Chinese patients
5. Inclusion criteria	none mentioned
6. Exclusion criteria	none mentioned
7. Comparability of complaints	knee pain
8. Pre-treatment diagnostics	Pain of the knee at rest, movement and pressure. Knee swelling. Improvement and therapeutic utility rating.
9. Treatment group	Received for four weeks daily 6 capsules with 1500mg GS and 3 placebo tablets
10. Control group	Received for four weeks daily 3 tablets with 1200mg IBU and 6 placebo tablets
11. Method of statistical analysis	Describitve statistics by conventional methodes. Mann-Whitney U test and Wilcoxon to evaluate the significance of differences.
12. Randomization	Yes
13. Double blinding	Yes
14. Treatment described	Yes

15. Referrence treatment described	Yes
16. Comparison with established treatment	Compared to IBU (1200mg daily)
17. Comparison with placebo	No
18. Contamination	Not mentioned
19. Drop-outs	GS group: 1 drop out, not related to therapy IBU group: 9 drop outs, related to drug therapy
20. Measurement of outcome:	Knee pain at rest
21. Duration of study	4 weeks
22. Duration of follow up	2 weeks
23. Conclusion	GS is a selective drug for OA, as effective on the symptoms of the disease as NSAIDs but significantly better tolerated. For these properties GS seems particularly indicated in the long-term treatments needed in OA.

Most important points:

- Short study and follow up period
- No word lost about homogeneous study group
- No radiographs taken
- No inclusion nor exclusion criterias mentioned
- Weakest performed study of those selected

➢ Lacks some essential aspects. Therefore, room for improvement.

V. Summary

As one can see in these studies, clinical trials with putative disease-modifying drugs for osteoarthritis can be problematic: long-term studies are difficult to perform, while the short-term studies often suffer from several methodological problems.

A joint working group of the World Health Organization's Regional Office for Europe and the European League Against Rheumatismus (EULAR) once suggested that the duration of these studies should be at least 3 years and if possible 5 years. They should be conducted according to a controlled , randomized, double-blind and parallel-group design (10).

Generally speaking, the most common problems associated with these clinical trials of disease-modifying drugs in osteoarthritis can be summarized into the following categories:

- number of patients,
- experimental design,

- diagnosis,
- disease status,
- evaluation criteria and end-points.

Number of patients

In most instances – except for the study done by Noack et al (8) - the number of patients necessary to show statistically sound results is not calculated. This implies that most of the trials are performed with an insufficient number of patients. Furthermore, patients who do not complete the trial might be reported but are not included in the analysis, i.e. the "intention-to-treat" approach is not frequently applied – except, once again, for the study done by Noack et al (8).

Experimental design

Several items are essential in this regard. First of all the study should be controlled, and preference should be given to placebo, at least for the characterization of the drug effect. The trial should be randomized, but this is an essential requirement in any clinical study in order to avoid a bias in the allocation of treatments. Also, preference should be given to double-blind procedures whenever possible: this of course will depend on the characteristics of the study medications and on the possibility of not recognizing one drug from another just because of other clearcut effects, such as adverse reactions or biochemical changes. Finally, the "parallel group" design should be preferred to "cross-over" studies, because of the high placebo effect, the drug given in the first arm of the cross-over has a higher probability to get benefit from this situation, a problem that can be partly overcome by randomization.

Most of these points are fulfilled in the analysed studies. Only Qiu in his study did not use a placebo. His study was not of a parallel-group design, too.

Diagnosis

The diagnosis of osteoarthritis is not difficult, provided that we have defined what we mean exactly by "osteoarthritis". In any case, for clinical research purposes classification criteria should be adopted in order to assure consistency of the patients enrolled in the trial. Sets of criteria have been published for classical osteoarthritis localizations by Lequesne and by the American College of Rheumatology (10). When symptom evaluation is important, the hip and the knee are among the best joints to be studied, since other localizations are less consistently painful.

Disease status

Once the diagnosis of the disease has been established, appropriate clinical and objective staging, as for example radiological classification, should be adopted and carefully reported, in order to assure homogeneity of patients and to know the population to which the results will be transferable. Patients should be over the age of 50 in order to avoid an insufficiently homogeneous population and a difference in disease progression for younger subjects. Secondary osteoarthritis should be excluded and a preference should be given to gonarthrosis, because of the existence of well standardized imaging techniques for this localization (10).

Evaluation criteria and end points

For objectiv results we need tests and indices that are reproducible and definitely allow the clinical efficacy evaluation in short-term and long-term trials.

Examples already exist and one of these is the Lequesne index of severity for knee or hip osteoarthritis. This is a combined score dealing with pain, maximum walking distance and movement limitation in some activities of daily living. It has been validated, in that inter-observer reproducibility is good and in drug trials it yields a finer score difference than conventional indices. Unfortunately, the Qui only uses knee pain as a criteria. On the other hand, the two other studies use multiple criterias – including the Lequesne index – for evaluation.

Finally it is important, according to evaluation criteria that have been chosen, to decide the efficacy end point of the study before it is started, so to allow the statistical plan a priori as well as the calculation of the sample size necessary to reach statistical significance.

VI. Conclusion

The main goal of therapy of OA is to relieve pain. There are currently a number of effektive medications that can accomplish this goal, but none are ideal for every patient and their use is limited by serious long-term toxicities. The use of NSAIDS, for example, is also limited by the fact that they do not necessarily change the natural course of the disease. Moreover, there is growing evidence and concern that long-term therapy with these agents may accelerate joint deterioration. Therefore, a better solution to this problern would be to develop a medication that would prevent or, at the very least, slow the progression of the disease and produced few adverse effects. Animal and human studies seem to suggest that glucosamine sulfate may be an ideal candidate that can provide these therapeutic benefits. Based on the currently published results of a small number of short-term trials, it is difficult to make any firm recommendations regarding the role of glucosamine sulfate in the treatment of OA. However, there appears to be increasing evidence suggesting that this agent may provide several therapeutic benefits for patients with OA (11). These include a progressive and gradual reduction of articular pain and tenderness, improved mobility, a lack of significant toxicity with short-term use, and sustained improvement after drug withdrawal. These benefits were significantly better than those of placebo (12) and, in some instances, equal to or slightly better than traditional therapies for OA.

The primary criticism against the use of glucosamine sulfate is that there are no rigorously conducted long-term studies evaluating its therapeutic benefits or toxic effects in patients with OA. According to McAlindon (11), most, of the trials published to date have serious design flaws or insufficient details to make adequate assessments. Moreover, there are no published trials examining the effects of glucosamine sulfate (or other glucosatmine salts) in any other forms of arthritis. Questions regarding product purity the most effective dose, or longterm adverse effects of glucosamine remain to be answered (12). Studies investigating glucosamine sulfate in combination with traditional OA therapies have not yet been performed, too.

Despite these controversies, patients with OA will undoubtedly seek alternative forms of therapy, especially when there are serious concerns about adverse effects. While studies conducted with glucosamine sulfate show some promise for the treatment of OA, additional longterm, rigorously controlled and better designed clinical trials with larger numbers of patients are needed to fully elucidate the safety and efficacy of this agent (12). In the interim

patients should continue to follow standard treatment recommendations for OA such as weight control, exercise, proper use of medications, joint protection, and application of heat or cold.

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APPENDIX I: Overview on the fulfillments of the criteria by each article analysed

	Noack W.	Reichelt A.	Qiu GX.
Study type	Y	Y	Y
Study goal	Y	Y	Y
Homogenous subjects	Y	N	Y
Number of subjects	Y	Y	Y
Inclusion criteria	Y	Y	N
Exclusion criteria	Y	Y	N
Comparability of compl.	Y	Y	Y
Pre-treatment diagnostics	Y	Y	Y
Treatment group	Y	Y	Y
Control group	Y	Y	Y
Method of statistics	Y	Y	Y
Randomization	Y	Y	Y
Double blinding	Y	Y	Y
Treatment described	Y	Y	Y
Reference treatment descr.	Y	Y	Y
Comparison w. estab. tre.	N	N	Y
Comparison with placebo	Y	Y	N
Contamination	Y	Y	N
Drop-outs	Y	Y	Y
Measurement of outcome	Y	Y	Y
Duration of study	Y	Y	Y
Duration of follow-up	N	Y	Y
Conclusion	Y	Y	Y
Total	Y=21 N=2	Y=21 N=2	Y=19 N=4

Y= criterion fulfilled N= criterion not fulfilled

APPENDIX II: GAG-Synthesis (taken from the article written by Gottlieb MS)

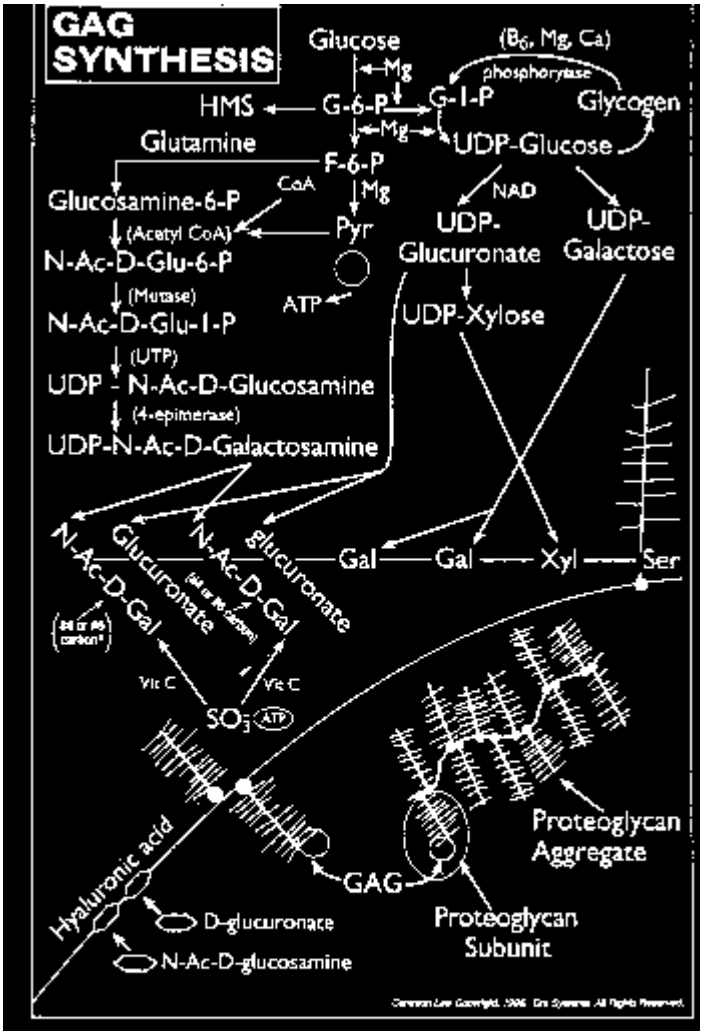

Fig. 6 *GAG synthesis occurs as a by-product of glycolysis. Note the essential vitamins and minerals necessary for catalyzing the reactions and conversions of the substrates. Improper diet and insufficient nutrition play an important role in the demise of cartilage and perpetuation of osteoarthritis. Conversely, vitamins and minerals are necessary for the production of glucosamine and maintenance of healthy joint cartilage. (Reproduced with permission.)*