

Evaluation of Glucosamine Sulfate Compared to Ibuprofen for the Treatment of Temporomandibular Joint Osteoarthritis: A Randomized Double Blind Controlled 3 Month Clinical Trial

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ABSTRACT. Objective. To compare the treatment potential of glucosamine sulfate (GS) and ibuprofen in patients diagnosed with temporomandibular joint (TMJ) osteoarthritis (OA).

Methods. Forty women and 5 men received either GS (500 mg tid) or ibuprofen (400 mg tid) for 90 days in a randomized double blind study. Assessment: TMJ pain with function, pain-free, and voluntary maximum mouth opening. Brief Pain Inventory (BPI) questionnaire and masticatory muscle tenderness were performed after a one week washout and at Day 90. Acetaminophen (500 mg) dispensed for breakthrough pain was counted every 30 days to Day 120.

Results. In total, 176 adults were interviewed, 45 (26%) qualified, 39 (87%) completed the study (21 GS, 18 ibuprofen). Four discontinued due to stomach upset (3 ibuprofen, one GS), one due to dizziness (GS), one due to inadequate pain control (ibuprofen). Within-group analysis revealed significant improvement compared to baseline of all variables in both treatment groups but no change in acetaminophen used. Fifteen GS (71%) and 11 ibuprofen (61%) improved, with positive clinical response taken as a 20% decrease in primary outcome (TMJ pain with function). The number of patients with positive clinical response was not statistically different between groups ($p = 0.73$). Between-group comparison revealed that patients taking GS had a significantly greater decrease in TMJ pain with function, effect of pain, and acetaminophen used between Day 90 and 120 compared with patients taking ibuprofen.

Conclusion. GS and ibuprofen reduce pain levels in patients with TMJ degenerative joint disease. In the subgroup that met the initial efficacy criteria, GS had a significantly greater influence in reducing pain produced during function and effect of pain with daily activities. GS has a carryover effect. (J Rheumatol 2001;28:1347–55)

Key Indexing Terms:

TEMPOROMANDIBULAR JOINT
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Osteoarthritis (OA) is a degenerative disease of synovial joints characterized by a progressive loss of normal structure and function of articular cartilage. OA brings discomfort and disability to millions of North Americans each year and the costs involved in treating OA are expected to reach 1% of the United States gross national product in year 2000¹. Its pathogenesis, although correlated to joint use, age, and “wear and tear,” remains uncertain.

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The temporomandibular joint (TMJ) is not immune in development of OA [also referred to as degenerative joint disease (DJD)] and a recent review reports roughly 8% to 12% of patients seeking treatment at temporomandibular dysfunction clinics receive a diagnosis of DJD². Once the diagnosis is made and if pain is an issue, the clinician generally places the patient on a soft diet, advises jaw functioning within a pain-free range, and prescribes a nonsteroidal anti-inflammatory drug (NSAID)². NSAID such as ibuprofen have traditionally been the medicines of first choice^{3,4}.

NSAID have a well documented record of relieving pain and reducing inflammation. Unfortunately, many of these medications are known to cause multiple side effects, notably upper gastrointestinal (GI) damage⁵. It has been reported that 14.6% to 43.9% of patients with OA treated with traditional NSAID develop gastric ulcers after 6 months of therapy⁶. Epidemiological and clinical studies report that the cost of NSAID treatment should be multiplied by a coefficient range of 1.36 to 3 when the cost of treating the induced GI damage is also taken into account⁷.

The risk of NSAID side effects may be less in the temporomandibular OA population, which are younger and usually receive analgesic doses.

There is now a growing body of evidence that many of the more traditional NSAID exacerbate the loss of the articular cartilage necessary for joint health by inhibiting proteoglycan synthesis at the level of the chondrocyte⁸⁻¹². This problem has prompted research into medicinal agents that have cartilage sparing, regenerative capacities and pain relieving effects.

Glucosamine is a naturally occurring aminomonosaccharide in the human body, biosynthesized from glucose and used to form glycosaminoglycan, a constituent of proteoglycans, an important component of the extracellular matrix of articular cartilage¹³. Its potential as a therapeutic agent for OA was first reported in 1969¹⁴. Investigations in the early 1980s found that patients with OA of the knee reported gradual and progressive reduction of articular pain and tenderness and improvement in the range of motion when administered glucosamine sulfate (GS) compared to placebo¹⁵⁻¹⁸. Oral administration of GS has also been reported to not irritate the GI tract¹⁹ and may stimulate the production of protective gastric mucoproteins²⁰. Several studies have also reported that therapeutic benefits of GS were maintained for weeks after therapy was discontinued^{21,22}.

GS is regarded as a food supplement and is available in health food and drug stores. Its potential as an adjunctive medicine for OA is gaining growing acceptance, supported by tissue, animal, and human studies (see Discussion). As in other joints, traditional pharmacological methods for treating patients with OA of the TMJ have largely depended on NSAID²³. Food supplements like GS may provide symptom relief for this patient population without the inherent side effects of nonselective cyclooxygenase (COX) NSAID. To date there are no published clinical trials to assess the efficacy of GS in treatment of patients with DJD of TMJ with pain. The articular surface of the TMJ is composed of a dense fibrous connective tissue (also referred to as fibrocartilage) and direct comparison to other synovial joints with hyaline cartilaginous articular surfaces may not be appropriate. Thus we investigated the potential of GS for treating patients diagnosed with TMJ DJD with pain.

MATERIALS AND METHODS

Forty-five individuals from a total of 176 interviewed (156 women, 20 men) over a 16 mo period were diagnosed with DJD of one or both TMJ and were deemed eligible to participate in this study. Participants were either patients of our Orofacial Pain Clinic at the University of Alberta or were recruited via mail to dentists in the Edmonton area or through local newspaper advertisement. Of the women not recruited (116), 45 did not show radiographic evidence of OA, 30 had inadequate pain levels, 10 reported allergy to NSAID, and 31 did not proceed for radiographic assessment. Of the men not recruited (15), 10 did not show radiographic evidence of OA, 3 had inadequate pain levels, and 2 reported allergy to NSAID. In addition to the inclusion criteria for this study (Table 1), patients met the

Table 1. Inclusion criteria

Baseline pain intensity \geq 3/10 VAS
Women or men \geq 18 years of age and willing to give informed consent
Women neither pregnant nor nursing
Degenerative joint disease not as a result of acute trauma, previous infection, or general joint/muscle disease (e.g. rheumatoid arthritis)
No history of intraarticular joint injections (e.g., steroids or hyaluronic acid)
No previous use of glucosamine and/or chondroitin sulfate
No history of congestive heart failure, renal disease, hepatic disease
No history of hypersensitivity to NSAID
No history of peptic ulceration or GI bleeding
No history of coagulation disorders
No active dental disease, periodontal disease, oral infection or pathology
If using an antidepressant or anxiolytic medication it must have been for at least 6 months
If using an occlusal splint it must have been for at least 3 months
Willing to take oral medication
Willing to undergo a one week washout period
Able to understand English

diagnostic criteria for DJD established by the American Board of Orofacial Pain²⁴ including radiographic evidence of DJD [structural change (subchondral sclerosis, osteophytic formation, erosion) and joint space narrowing (confirmed by polycycloidal axially corrected tomographic radiographs — Tomax; Incubation Industries Inc., Warrington, PA, USA) and a minimum mean pretreatment visual analog scale score of 3/10 for TMJ pain on function (pain on chewing, yawning, laughing, talking)]. Score of 3 was used since it is considered the lower boundary in establishing a moderate pain level for a 1 to 10 VAS scale²⁵, and moderate pain levels are required before administration of analgesic agents to ensure adequate sensitivity of treatment effect²⁶. Informed consent was obtained from all patients.

This study was conducted in a double blind manner. Neither patients nor investigators knew which of the 2 medications was administered until the end of the study, and medications were prepared and coded as identical clear capsules by a pharmacist from batches that came with certificate of analysis of ingredients to ensure uniformity throughout. JamiesonTM (Windsor, Ontario, Canada) and Apotex Co. (Toronto, Ontario, Canada) kindly donated GS and ibuprofen, respectively. There was no drug crossover since carryover effects have been reported for GS^{21,22}. There was a one week pretreatment washout period for all patients to eliminate the potential effects of previously used NSAID and/or analgesics. Patients were then block randomized into one of the 2 treatment groups, GS (500 mg) and ibuprofen (400 mg). Block randomization ensures that the number of participants is equally distributed among the treatment groups over the course of the study. Our statistician (NGP) generated the randomization sequence. Participants were instructed to take the medication q8h with food and allowed only acetaminophen tablets (500 mg, 1–2 q4–6h prn, maximum 4000 mg/day) for breakthrough pain. All outcome variables were measured twice — at baseline (after 7 day washout period) and again at Day 90. Patients returned every 30 days to count acetaminophen used, and were given study medication for the next 30 days.

The primary clinical outcome was 20% or greater reduction in joint pain with function (chewing, yawning, talking, laughing) measured using a modified VAS, the colored analog scale (CAS) developed by McGrath, *et al*²⁷. The CAS, used in pediatric pain, is a modification of the VAS, a valid and reliable pain measurement tool²⁸⁻³⁰.

Secondary outcomes measured were as follows. (1) Pain-free and voluntary maximum interincisal opening, measured with a 100 mm ruler. (2) Brief Pain Inventory questionnaire, a valid and reliable questionnaire that measures pain intensity and effect (interference) on quality of life³¹. Intensity (worst and least pain in the last week, average pain, pain right now) recorded on numerical scales from 0 (no pain) to 10 (pain as bad as

you can imagine). The effect of the pain was recorded in terms of how much it interferes with general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life, recorded on a numerical scale from 0 (does not interfere) to 10 (completely interferes). Permission to use this questionnaire was given by Dr. Charles S. Cleeland, March 9, 1998. (3) Extraoral masticatory muscle tenderness (7 equivalent sites bilaterally, total of 14) was assessed using a pressure threshold meter (i.e., an algometer or dolorimeter) with palpation sites located according to Kim, *et al*³². Muscles assessed were the anterior, middle and posterior temporalis, anterior, inferior and deep masseter, and medial pterygoid. The pressure threshold meter is used to determine the pressure pain threshold (PPT), the minimum pressure (force) inducing discomfort or pain. Validity³³⁻³⁶ and reliability^{33,34,37,38} of this measure have been reported. The pressure threshold meter used was the Baseline® push/pull dynamometer (GNR Orthopaedic and Rehabilitation Products, Ocala FL, USA), a hand held force gauge fitted with a soft rubber disk with a surface area of 1 cm². The gauge is calibrated in kg/cm², with a range to 5 kg and 50 g divisions. The recording procedure as described³⁹ consists of placing the tip of the gauge perpendicular to the site of interest, and increasing the pressure at a rate of 1 kg/second. The pressure was stopped and the gauge removed for reading when the patient says "yes," indicating her/his pressure threshold. PPT values (kilopascals) for masticatory muscles of specific interest in our study have been reported in women and men without history of headache or facial or neck pain⁴⁰. We used the mean minus one standard deviation values reported by Chung, *et al*⁴⁰ and converted them to kg/cm² units according to the formula $\text{kg} = 0.0102 \times \text{kPa/kPa}$. Readings obtained in our study that were equal to or less than these "normal" PPT values were noted as positive responses, and those equal to or greater than normal values were noted as negative responses. A value of 1 is assigned for each positive response and 0 for each negative response. In this way a palpation index similar to that described by Friction, *et al*⁴¹ for masticatory muscles was used to assess muscle tenderness. The index used in our study is the sum of the positive responses out of the total number of sites (in this case 14). Side effects reported by patients were recorded as the last step in data collection.

Yates' corrected chi-square was used to compare proportions of subjects who had functional pain improvement at variable clinical levels of significance. In instances where the number of respondents was less than 5 Fisher's exact tests were used. Frequency distributions for the major outcome variables were plotted to ensure normality. Statistical analysis involved paired t tests for within-group analysis and independent sample t tests for between-group analysis. Statistical significance was set at $\alpha = 0.05$. Data were analyzed using SPSS software, version 9.0 for Windows.

The University of Alberta Ethics Committee approved this study April 1998.

RESULTS

One hundred seventy-six patients were interviewed for this study from August 1, 1998, to November 1, 1999. The most common reason for exclusion was the lack of radiographic evidence of DJD (31%). Of the 45 patients that qualified (mean age 37.5 yrs; 40 women, 5 men), 39 (87%) completed the study (21 GS, 18 ibuprofen). Of 39 patients that completed the study none reported adverse effects from either medication. Four patients (8.8% of 45) taking ibuprofen and 2 (4.4% of 45) taking GS discontinued due to side effects. Three of 4 dropouts in the ibuprofen group discontinued due to stomach upset (dropout at Day 7 for 2 of these, Day 57 for the other), the other due to inadequate pain control (dropout at Day 64). One dropout in the GS group was due to dizziness (dropout Day 43), the other due to stomach upset (dropout Day 34).

There were no significant differences between treatment groups in terms of demographic characteristics or measured variables at the start of the study (Table 2).

When all patient data were analyzed, there were significant improvements from baseline (Day 0) to Day 90 for all variables measured (except acetaminophen used) for both treatments (Table 3).

Six (29%) patients taking GS and 7 (39%) taking ibuprofen did not respond when clinical significance was set as a 20% improvement in TMJ pain with function. There was no significant difference ($p = 0.73$) between groups in the number of patients who met the primary endpoint 20% reduction in functional pain. Between-group analysis of differences for patients showing at least 20% reduction in functional pain revealed that participants taking GS improved significantly more in terms of functional pain evaluation and overall pain interference than those taking ibuprofen (Table 4). In addition, patients that had taken GS used significantly less acetaminophen than the ibuprofen group from Day 90 to 120.

Table 2. Demographic and measured variables at baseline.

Variable	Glucosamine Sulfate, n = 21	Ibuprofen, n = 18	Observed Mean Difference Between Treatments	p
Demographics				
Age, mean, yrs (SD)	36.62 (10.30)	38.73 (13.30)	-2.11	0.55
Disease duration, mean, mo (SD)	16.61 (8.06)	15.09 (8.01)	1.52	0.53
Measured variables				
Functional pain evaluation, mean, VAS (SD)	23.18 (6.53)	19.52 (6.74)	3.66	0.09
Pain-free mouth opening, mean, mm (SD)	24.71 (9.25)	26.06 (8.12)	-1.34	0.64
Voluntary mouth opening, mean, mm (SD)	34.52 (7.26)	37.39 (7.46)	-2.87	0.23
BPI questionnaire				
Pain intensity, mean, VAS (SD)	22.67 (5.34)	19.36 (7.65)	3.31	0.13
Pain interference, mean, VAS (SD)	32.26 (13.26)	25.19 (14.79)	7.07	0.12
Extra oral masticatory muscle pain, mean, positive on 14 sites (SD)	7.81 (5.07)	8.00 (5.43)	-0.19	0.91

Table 3. Comparison between Day 90 and baseline for both treatments.

Variable	Mean Difference (SD)*, Glucosamine Sulfate, n = 21	Coefficient of Variation (SD/mean), Glucosamine Sulfate, n = 21	p	Mean Difference (SD)*, Ibuprofen, n = 18	Coefficient of Variation (SD/mean), Ibuprofen, n = 18	p
Functional pain evaluation, VAS	-10.50 (10.79)	1.03	< 0.001	-5.93 (5.83)	0.98	< 0.001
Pain-free mouth opening, mm	10.14 (11.09)	1.09	< 0.001	8.39 (7.42)	0.88	< 0.001
Voluntary mouth opening, mm	7.14 (7.48)	1.05	< 0.001	4.06 (5.38)	1.32	< 0.001
BPI questionnaire						
Pain intensity, VAS	-10.00 (8.92)	0.89	< 0.001	-7.31 (5.91)	0.81	< 0.001
Pain interference, VAS	-15.07 (13.68)	0.91	< 0.001	-8.33 (11.68)	1.40	0.016
Extra oral masticatory muscle pain (positive on 14 sites)	-3.95 (3.89)	0.99	< 0.001	-4.33 (4.54)	1.05	0.006
Acetaminophen (tablets/day)						
Day 30 to 60	-2.95 (10.04)	3.40	0.193	1.78 (11.39)	6.40	0.517
Day 60 to 90	3.14 (10.95)	3.48	0.203	1.83 (9.34)	5.10	0.941
Day 90 to 120	-1.24 (18.49)	14.91	0.762	2.94 (20.37)	6.92	0.548
Total at 90 days	65.24 (53.05)	0.81	< 0.001	63.39 (66.18)	1.04	0.001

*Day 90 value minus beginning of study value.

Table 4. Between-treatment group comparison at Day 90 with clinical significance set at 20% improvement in functional pain.

Variable	Mean Difference (SD)*, Glucosamine Sulfate, n = 15	Coefficient of Variation (SD/mean), Glucosamine Sulfate, n = 15	Mean Difference (SD)*, Ibuprofen, n = 11	Coefficient of Variation (SD/mean), Ibuprofen, n = 11	p	Estimated Power at Observed Values
Functional pain evaluation, VAS	-15.19 (8.92)	0.59	-8.30 (4.49)	0.54	0.017	0.62
Pain free mouth opening, mm	12.93 (11.62)	0.90	9.00 (8.67)	0.96	0.354	0.15
Voluntary mouth opening, mm	8.33 (8.10)	0.97	6.46 (5.94)	0.92	0.521	0.10
BPI questionnaire						
Pain intensity, VAS	-13.13 (8.33)	0.63	-8.23 (4.89)	0.59	0.095	0.39
Pain interference, VAS	-19.50 (12.32)	0.63	-8.64 (14.27)	1.65	0.049	0.51
Extra oral masticatory muscle pain (positive on 14 sites)	-4.13 (3.74)	0.91	-4.64 (5.26)	1.13	0.778	0.06
Acetaminophen (tablets)						
Day 30 to 60	-3.53 (10.68)	3.02	-1.82 (11.44)	6.29	0.540	0.09
Day 60 to 90	1.80 (9.68)	5.38	-2.18 (7.68)	3.52	0.271	0.19
Day 90 to 120	-5.00 (13.02)	2.60	8.55 (10.59)	1.24	0.009	0.78
Total at 90 days	59.33 (51.49)	0.87	42.27 (69.35)	1.64	0.478	0.11

* Day 90 value minus beginning of study value.

With clinical significance for functional pain improvement $\geq 20\%$ no significant differences were found between the 2 treatment groups other than when set at $> 80\%$ (Table 5).

DISCUSSION

Over the past 5 years public interest in GS for treatment of OA has increased due in part to 2 publications, *The Arthritis Cure*⁴² and *Maximizing the Arthritis Cure*⁴³. The lack of interest in GS by researchers and pharmaceutical companies in general has been attributed by some to the fact that glucosamine is a natural product that cannot be patented⁴⁴.

The potential of glucosamine as a therapeutic agent for OA was first reported in 1969 by a German physician¹⁴.

Table 5. Percentage functional pain improvement at variable clinical levels of significance.

Set Clinical Level of Significance	Glucosamine Sulfate, n = 21 (%)	Ibuprofen, n = 18 (%)	p
Negative response	4 (18)	4 (22)	1.000**
0 to 19	17 (81)	14 (78)	1.000*
20 to 39	15 (71)	11 (61)	0.733*
40 to 59	10 (48)	5 (28)	0.347*
60 to 79	6 (29)	3 (17)	0.464**
80 to 100	4 (19)	0 (0)	0.110**

* Yates' corrected chi-square was used to compare proportions in both groups unless one of the fitted cells had a value of < 5 , and in this case

**Fisher exact tests were used.

Later other German investigators⁴⁵⁻⁴⁷ reported decreases in pain often accompanied by increased mobility when patients received a 400 mg solution of GS administered once daily intravenously, intramuscularly, or intraarticularly. These results should not be considered definitive since they were uncontrolled studies. Numerous controlled, double blind investigations evaluating glucosamine (oral, intramuscular, or intravenous administration) versus placebo in patients diagnosed with OA of the knee were carried out¹⁵⁻¹⁸. All studies reported gradual and progressive reduction of articular pain, joint tenderness, and swelling and improvement in the range of motion. A double blind 8 week study involving 40 patients with knee OA found that GS 500 mg tid was as effective as ibuprofen 400 mg tid in relieving pain after the first 2 weeks, and by the end of the trial was more effective⁴⁸. Although these studies reported improvement in symptoms when patients with knee OA were administered glucosamine, there were limitations in study design that included using hospitalized patients undergoing active physiotherapy, blinding placebo injections, and short study times. These studies have been critically reviewed⁴⁹⁻⁵³.

A number of articles on GS have been published within the last decade. Muller-Fassbender and colleagues⁵⁴ in a double blind 4 week trial randomized 200 patients with knee OA. These researchers found oral GS (500 mg tid) as effective as ibuprofen (400 mg tid) from the second week of treatment, and no difference was found between groups with respect to the magnitude of response. Adverse events were reported in 35% of the ibuprofen group, but in only 6% of the GS group, with fewer dropouts in the latter. Qiu, *et al*⁵⁵ in a similar 4 week trial of 178 Chinese patients found both GS (1500 mg daily) and ibuprofen (1200 mg daily) significantly reduced the symptoms of knee OA, with a trend toward GS to be more effective. The GS group reported fewer adverse reactions (6%) compared to ibuprofen (16%) and there were no dropouts in the GS group compared to 10% in the ibuprofen group. Noack and colleagues⁵⁶, in a 4 week placebo controlled study of 252 patients with knee OA, reported patients that had taken GS 1500 mg/day orally showed significant improvement in the Lequesne index compared to the placebo group. Reichelt, *et al*²¹ compared treatment of GS 400 mg intramuscularly twice per week for 6 weeks with placebo injections administered on the same schedule in 155 patients with knee OA. Fifty-five percent of patients who received GS and 33% of those given placebo responded as judged by the Lequesne index.

In the most recent study published, patients with knee OA in an 8 week double blind study were given either glucosamine hydrochloride 500 mg tid ($n = 41$) or placebo ($n = 48$)⁵⁷. No statistically significant difference was found between groups in the primary endpoint measured [Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain score] between Week 0 and Week 8. However, significant differences were found in secondary

endpoints from Week 5 to Week 8 (daily diary and knee examination) that suggested that glucosamine hydrochloride benefits some patients with knee OA.

There has been only one report of GS for patients with TMJ OA⁵⁸. The primary outcome of that study of 50 patients was a reduction in joint noise. All patients received glucosamine hydrochloride (1600 mg bid), 1000 mg of calcium ascorbate (1000 mg bid), and a mixture of chondroitin sulfate-4 and chondroitin sulfate-6 (1200 mg bid). After an undefined period of time 80% of patients reported a reduction in joint noise. Unfortunately, this study does not indicate treatment time (other than patients were reevaluated every 2–3 weeks) and cannot distinguish which of the co-administered supplements influenced outcome the most. In addition, the influence of either occlusal splint therapy introduced during the study for “many” patients or ibuprofen and aspirin permitted (counts not reported) when joint pain and/or swelling interfered with daily routines and activities on the primary outcome is unclear. This study was neither randomized nor blinded. Reducing joint noise as a primary treatment outcome for patients with TMJ disease is questionable and the value of this study is uncertain.

Our study was designed to establish whether the food supplement GS, reported to help the symptoms of knee OA, will improve symptoms in patients diagnosed with OA of the TMJ when compared to a more traditional pharmacological agent for OA. An analgesic dose of ibuprofen (1200 mg) rather than an antiinflammatory dose (1800–2400 mg) was used in this study. This choice was based on desire to minimize the risk associated with NSAID therapy by minimizing the daily dose, and on reports of studies that suggest the reduction in symptoms with NSAID therapy results from their analgesic rather than antiinflammatory properties^{59,60}. An overall $\geq 20\%$ decrease in TMJ pain with functioning (chewing, yawning, talking, laughing) was our primary clinical outcome, since a decrease in pain on function is often a primary reason patients present for treatment at our clinic. Important secondary issues that often arise due to TMJ OA are decreases in pain-free and voluntary mouth opening and masticatory muscle tenderness. Patients also report symptoms that fluctuate in severity over time and interfere with their daily functioning. All these secondary issues were addressed in this study.

We found that GS decreased TMJ pain on function, increased pain-free and voluntary mouth opening, and decreased the severity and interference of the pain on daily functions. Similar results were seen for the ibuprofen treatment group, but improvement in functional pain was significantly less than in the GS treatment group and patients in the ibuprofen group found no significant improvement from the start of the study in terms of how the pain interfered with daily activities.

Both treatment groups used roughly equivalent amounts of acetaminophen for breakthrough pain during the study,

but once study medication was discontinued the ibuprofen treatment group needed significantly more acetaminophen over the ensuing 30 days. This may be attributable to ibuprofen's ability to help symptoms only while a therapeutic dose is maintained and to a carryover effect for GS, as reported^{21,22}.

Clinicians are often asked by patients, "How much will this medication help my joint pain and are there any side effects." Our results indicate that about 50% of patients that are prescribed GS will achieve at least a 50% reduction in their joint pain on function and 70% of patients at least a 39% reduction of their pain (Table 5). Side effects and dropouts in this study are comparable to other reports comparing GS and ibuprofen. In general one can expect few side effects when taking GS and these will mainly consist of minor GI problems.

Most if not all clinical trials of GS make no reference to the purity of the glucosamine used. To overcome this limitation all GS capsules we used were compounded from the same batch, which came with a certificate of analysis. The certificate of analysis included spectral analysis, physical properties, microbiology, and potency of the GS. In regard to the latter each GS capsule had 467.2 mg of GS per 500 mg capsule. The assay test for GS was reported as 101.1%.

OA of the TMJ is a prevalent and serious health care issue. Eight to 12% of patients that present to a TMJ and orofacial pain clinic receive a diagnosis of this disease². These patients tend to be young women in their second and third decades⁶¹⁻⁶³, ages we consider the most fruitful and productive. In addition, signs and symptoms of TMJ degenerative disease can occur in early childhood⁶⁴. Professionals treating OA of the TMJ face dilemmas similar to those of physicians treating OA of other joints in terms of what is best to prescribe when pharmacotherapy is necessary. For the most part decisions have been based on knowledge acquired from research on joints other than the TMJ. Can we assume that "knowledge of OA in other synovial joints is appropriate to apply to the TMJ"⁶⁵?

Fundamental differences exist between the TMJ and other synovial joints. A major difference is that the articular surface of the TMJ (mandibular condyle and the temporal fossa) is not cartilage but a dense fibrous connective tissue (also referred to as fibrocartilage) that consists primarily of type I collagen⁶⁶ rather than the type II seen in hyaline cartilage⁶⁷. Water constitutes over 65–70% of the total weight of hyaline cartilage⁶⁷ and is reported to be lower in TMJ fibrocartilage⁶⁵. Chondrocytes distributed throughout the extracellular matrix account for roughly 2%–3% of the total tissue volume in hyaline cartilage⁶⁷, but only 0.01%–0.1% of the total tissue volume in TMJ articular fibrocartilage⁶⁸. The articular tissue of the TMJ consists mainly of fibroblasts, not chondrocytes, as in hyaline cartilage⁶⁶. In hyaline cartilage, the glycosaminoglycan (GAG) chains of proteoglycans consist of 90% chondroitin 4- and 6-sulfate and

keratin sulfate⁶⁷. TMJ fibrocartilage's dermatan sulfate content has been cited as being higher, whereas keratan sulfate content is much lower⁶⁵.

Our results add to the literature advocating the use of GS in OA, but also to the controversy that exists with this food supplement. As of 1997, The Arthritis Foundation does not recommend the use of glucosamine as a treatment of OA⁶⁹. GS has been termed a "chondroprotective agent"^{70,71}, defined as "a substance able of increasing chondrocyte anabolic activity, while simultaneously suppressing the degradative action of mediators (cytokines, prostaglandins, proteinases) on cartilage"⁷⁰. However, this term has been considered misleading and inappropriate when applied to OA, since OA is a process of the entire joint, not only the articular cartilage⁷². The term disease modifying OA drug (DMOAD, also called structure modifying drugs for OA) has been used to describe "an agent that arrests or retards the progression of OA and/or enhances normal reparative processes in the diseased joint"⁷². To date, there have been no agents proven to have structure modifying properties in humans⁷³ and it is not known if GS has DMOAD activity. At this point it may be more appropriate to describe GS as a "symptom modifying agent" since improvement in joint pain is reported for most clinical trials to date and improvement in joint pain is recommended as the primary outcome measure for symptom modifying agents⁷³.

An *in vitro* study in the 1950s showed that glucosamine stimulated the uptake of $^{35}\text{SO}_4^-$, a marker of GAG synthesis by cartilage⁷⁴. GS has been found to significantly increase *in vitro* secretion of GAG by fibroblast cultures⁷⁵. Later research revealed that exogenous glucosamine increased the synthesis of GAG in cartilage cultures^{76,77}. More recently, studies using chondrocytes isolated from and cultured from human osteoarthritic femoral heads found that GS induced a significant and dose dependent increase of proteoglycan synthesis, but did not affect DNA synthesis or collagen type II or prostaglandin E_2 production by chondrocytes⁷⁸. With animal models of inflammation oral glucosamine was reported to protect rats from inflammation caused by several nonspecific foreign agents (dextran, formalin, and acetic acid) but did not exert activity against specific mediators of inflammation (histamine, serotonin, or bradykinin)^{19,79}. GS has no analgesic activity and is ineffective against proteolytic enzymes of inflamed tissues and against the biosynthesis of prostaglandins elicited from arachidonic acid or histamine^{19,79}. GS reduces superoxide radicals generated by macrophages and inhibits lysosomal enzymes and its effects are prostaglandin independent^{19,79}. Glucosamine's effects have been described as a prostaglandin independent, COX independent "antireactive" activity^{19,79}.

The biochemical events to explain symptom relief in patients taking GS are not completely known, but are perhaps only partially explained by GS's ability to act as a substrate and stimulant of GAG production within articular

cartilage. Has a focus on articular cartilage alone become a red herring? OA is a disease process of the entire joint that includes the synovial membrane and subchondral bone and not just the aneural articular tissues. Traditional NSAID decrease symptoms by inhibiting COX, but can also interfere with cartilage metabolism. GS induces cartilage metabolism and its effects are COX independent. Can symptom relief be entirely explained by the cartilage metabolism effects or are there secondary events such as inhibition of catabolic mechanisms of OA induced by proinflammatory cytokines such as interleukin 1 and tumor necrosis factor alpha that explain the effects of GS? This may warrant further research and provide more insight into the role of GS in OA.

This study evaluated whether GS would help the symptoms of TMJ OA. Our results, the first for the TMJ, indicate that GS has at least the same potential as a traditional medication prescribed for OA and temporomandibular disorders. It is too early, however, to make definitive conclusions on this food supplement — the limitations of this study are as follows: (1) Low statistical power, which would be improved with a larger study population — a post hoc analysis using sample standard deviation value computed from the data collected in our study, with 20% pain reduction as the primary outcome measure, revealed that a sample size of 82 patients would be necessary to attain power equal to 0.8. This would be a more suitable sample size for future comparative studies with GS. (2) This study used an arbitrary pain reduction of 20%, which may be considered a minimally important clinical difference. These results are promising, but a larger trial using a greater pain reduction value should be conducted. (3) Large variances in the results, perhaps attributable in part to psychological aspects known to influence the pain experience that are difficult to measure clinically. (4) No placebo control — although we did find that once patients taking GS discontinued this medication less acetaminophen was required for pain over an ensuing 30 days than the ibuprofen treatment group, which is not indicative of a placebo response.

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