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Efficacy of a combination of FCHG49™ glucosamine hydrochloride, TRH122™ low molecular weight sodium chondroitin sulfate and manganese ascorbate* in the management of knee osteoarthritis

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Summary

Objectives: The objective of this study was to evaluate the oral combination of glucosamine HCl, sodium chondroitin sulfate and manganese ascorbate for the treatment of osteoarthritis (OA) of the knee.

Design: A randomized placebo-controlled study design was implemented. We recruited 93 patients with OA of the knee from a single center. The intervention group received 1000 mg FCHG49™ glucosamine HCl, 800 mg TRH122™ low molecular weight sodium chondroitin sulfate and 152 mg manganese ascorbate twice daily (Cosamin®DS). Patients were evaluated initially and then every 2 months for 6 months. The primary outcome was the Lesquene Index of severity of osteoarthritis of the knee (ISK).

Results: Patients with radiographically mild or moderate OA ($N=72$) in the intervention group showed significant improvement in the ISK at 4 and 6 months ($P=0.003$ and $P=0.04$, respectively). The response rate to the medication was 52% vs a 28% response rate to placebo. Patients with radiographically severe osteoarthritis ($N=21$) did not show significant improvements in the ISK. There was a 17% incidence of adverse events in the intervention group and 19% in the placebo group.

Conclusions: The studied combination of glucosamine HCl, sodium chondroitin sulfate and manganese ascorbate was found to be effective for the treatment of radiographically mild to moderate OA of the knee as measured by the ISK. This is the first U.S. study of these agents.

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Key words: Glucosamine hydrochloride, Chondroitin sulfate, Knee joint, Osteoarthritis.

Introduction

The current medical management of osteoarthritis (OA) is largely palliative, focusing on the amelioration of pain and the suppression of inflammation, mostly through analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs).¹ NSAIDs do not improve the natural history of the disease. In fact, Dr Kenneth Brandt, in an article entitled 'Should NSAIDs be used for the treatment of osteoarthritis?', summarized data suggesting that some NSAIDs might even accelerate the degenerative process of OA because they might decrease glycosaminoglycan (GAG) synthesis.² These perplexities regarding the long-term use of NSAIDs, along with expanding knowledge on cartilage biochemistry and OA pathophysiology, have prompted research on a series of new agents that are being studied for their specific effects on this disease. Chondroitin sulfate and glucosamine are two of these agents.

Glucosamine is an amino-monosaccharide derived from chitin in crustacean shells. Studies indicated that glu-

cosamine stimulates the synthesis of proteoglycans^{5–7} as well as possessing anti-inflammatory activity in different animal models without inhibiting the synthesis of prostaglandins.^{3,4} Glucosamine exhibited no known toxicity at doses far in excess of those used in human clinical trials, as might be expected from a naturally-occurring substance. Compared to indomethacin, the therapeutic margin with regard to prolonged treatment is 10–30 times more favorable for glucosamine.⁴ Chondroitin sulfate extracted from bovine trachea is a long-chain polymer of repeating disaccharide units: galactosamine sulfate and glucuronic acid, and constitutes the majority of GAGs in articular cartilage. The proposed mechanisms of action of chondroitin sulfate in OA are: (1) contribution to the pool of GAGs in cartilaginous tissue; (2) inhibition of synovial degradative enzymes; and (3) stimulation of GAGs and collagen synthesis by chondrocytes.^{6–9} The studied combination also contained manganese which is a cofactor necessary for the efficient synthesis of proteoglycans.¹⁰ In order for these substances to be effective when given orally, they must be absorbed and reach the site where they work. Radiolabeled glucosamine given orally to six human volunteers was 90% absorbed.¹¹ Necropsy of dogs given oral radiolabeled glucosamine showed that glucosamine had a tropism for articular cartilage.¹² Radiolabeled chondroitin sulfate given orally to humans was also 70% absorbed.¹³ Its affinity for synovial fluid and articular cartilage has also been demonstrated.¹³ *In vitro*,^{5,7–9,14} and *in vivo*^{15–17} data suggest that these compounds may positively alter the natural history of OA.

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Although the American literature is devoid of human clinical data on these agents, there are copious data available from the European literature on glucosamine^{24–37} and on chondroitin sulfate.^{15,16,37–43} Only a small number of the previous studies had a randomized, double-blind, controlled design and studied only a single joint (such as the knee) and used a validated outcomes tool (such as the Lesquene index of severity of osteoarthritis of the knee, ISK). Muller-Fassbender *et al.*³² conducted a clinical trial of oral glucosamine and found it to be equally efficacious to ibuprofen in the treatment of OA of the knee. Ibuprofen worked more quickly than glucosamine but also had more side effects. Noack *et al.*³³ found that patients with OA of the knee on oral glucosamine had a decrease in the ISK significantly more than placebo. Response to the medication was defined as a drop in the ISK of 3 points and 52% of patients responded to glucosamine compared to 37% of patients responding to placebo ($P=0.016$). In a study of oral chondroitin sulfate for treatment of OA of the knee, Mazieres *et al.*⁴⁰ noted a significant drop of 3 points the ISK score in the intervention group compared to 1.5 points drop in the placebo group ($P<0.02$). Several other clinical studies confirmed its efficacy in OA patients.^{15,16,37–43}

It has been postulated that combining glucosamine with chondroitin sulfate yields a synergistic rather than additive effect^{45–47} because glycosaminoglycan production is stimulated by glucosamine and degradation is inhibited by chondroitin sulfate. This theory was supported in a recent study that showed that a combination of glucosamine and chondroitin was synergistic, having significantly higher effect than the additive effects of the individual ingredients.²² The purpose of this study was to evaluate the effectiveness of the studied combination of agents in the treatment of the symptoms of OA of the knee. This study did not address the question of whether or not they are disease-modifying agents nor did it assess the synergistic effect between the individual components.

Materials and methods

All patients were recruited from the principal investigator's orthopedic practice in Hendersonville, NC. Eight hundred and twenty-three patients responded to an article in the local newspaper on the intended study. These were a mix of osteoarthritic patients and 'self diagnosed' ones, so patients were first screened by mail using the criteria listed below.

EXCLUSION CRITERIA

These criteria included pregnancy, severe activity-limiting chronic diseases, non-insulin-dependent diabetes, alcoholism, history of significant hematological disorder, history of hepatic or renal impairment, active peptic ulcer, associated musculoskeletal disease other than OA, associated metabolic diseases, injury to or surgery on the involved knee within 6 months, intraarticular corticosteroids within the previous 2 months and regular use (more than three times a week) of NSAIDs during the previous 2 months. The occasional use of NSAIDs as rescue medication was accepted. Patients using NSAIDs regularly were given a 2-week trial period to use NSAIDs as a rescue medication before being admitted to the study.

INCLUSION CRITERIA

Patients not exhibiting any of the exclusion criteria were then evaluated using the Lesquene index of severity of

osteoarthritis of the knee (ISK).²¹ Patients with an ISK of at least 7 points were then evaluated radiographically. Weight bearing posteroanterior radiographs at 45° flexion were obtained for every patient by the same technician using a jig, which is a mechanical device used for consistent positioning of the patient. It assures 45° of flexion and centering of the knees on the X-ray film.¹⁸ Radiographs were assessed jointly by the principle investigator and a board certified radiologist using the Kellgren and Lawrence atlas.^{19,20} Individuals with grade 2 or more were eligible for the study. The reader will recall that Kellgren and Lawrence defined radiographic grades of osteoarthritis as grade 0=normal; grade 1=doubtful narrowing of joint space and possible osteophytic lipping; grade 2 (mild)=definite osteophytes and possible narrowing of joint space; grade 3 (moderate)=moderate multiple osteophytes, definite narrowing of joint space, some sclerosis, and possible deformity of bone contour; and grade 4 (severe)=large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour. Further inclusion criteria were as follows: both genders between 45 and 75 years of age, ability to walk, willingness to comply with the study protocol and arthritic symptoms of greater than 6 months duration. Patients meeting the above criteria were then accepted into the study and included in the intent to treat analysis after they had their baseline visit. Patients with both unilateral and bilateral OA were accepted. In patients with bilateral involvement, only the more symptomatic knee was studied. Ninety-three patients were accepted into the study. The primary goal of the study was to assess patients with Kellgren and Lawrence radiological grades 2 and 3. However, a surprising number of patients with grade 4 OA presented for the study. Since no other study had accepted or at least separately evaluated grade 4, it was elected *post hoc* to accept these patients to evaluate them separately.

Patients were allocated to the intervention ($N=46$) and placebo ($N=47$) groups using a randomized block design. The group assignment was generated before the start of patient recruitment. The randomization schedule was obtained using a computer-based pseudo-random number generator. Each bottle was given a sequential number (1,2,3, . . .) with the code concealed to the investigator. The sequential numbers were matched with the order of inclusion of eligible patients into the study. Neither the patient nor the evaluating physician was aware of the treatment assignment. After termination of the study, letters were sent to the principle investigator (Dr Das) with the treatment assignment in order to inform the patients. Compliance was measured by pill counts carried out by the interviewer at every visit.

Of the 46 patients randomized to the intervention group 33 had Kellgren and Lawrence grade 2 or 3 OA and 13 had Kellgren and Lawrence grade 4 OA. Of the 47 patients randomized to the placebo group 39 had Kellgren and Lawrence grade 2 or 3 OA and 8 had Kellgren and Lawrence grade 4 OA. Patients received two capsules twice a day orally. Each intervention capsule contained 500 mg FCHG49[™] glucosamine hydrochloride, 400 mg TRH122[™] low molecular weight sodium chondroitin sulfate, and 76 mg manganese ascorbate (Cosamin[®]DS, Nutramax Laboratories Inc., Baltimore, MD, U.S.A.). The glucosamine hydrochloride and sodium chondroitin sulfate were assayed by the School of Pharmacy at University of Maryland at 99% and 95% purity, respectively. The placebo group received indistinguishable capsules containing methyl-cellulose. Patients were evaluated initially and then

Table I
Demographics and characteristics of study patients (N=93)

	Placebo (N=47)	Intervention (N=46)	P-value
Age (years)*	66.0 (\pm 1.5)	64.5 (\pm 9.8)	0.5
Body mass index*	30.2 (\pm 0.9)	30.5 (\pm 1.0)	0.8
Male gender	10 (22%)	13 (28%)	0.4
Married	34 (72%)	38 (83%)	0.2
Season of recruitment in study			
—Fall	11 (23%)	10 (22%)	
—Winter	13 (28%)	16 (35%)	
—Spring	14 (30%)	13 (28%)	
—Summer	9 (19%)	7 (15%)	0.9
OA in other joints	21 (45%)	15 (33%)	0.2
Secondary OA	6 (13%)	7 (15%)	0.7
Severe OA	8 (17%)	13 (28%)	0.2
Weight change from baseline (lb)*	0 (\pm 1.2)	-0.7 (\pm 0.9)	0.8
Duration of OA in study-joint (years)*	7.4 (\pm 1.2)	5.6 (\pm 1.3)	0.3
Mean follow-up period (months)*	6.5 (\pm 0.1)	6.4 (\pm 0.1)	0.6

OA=osteoarthritis.

*Data presented are means (\pm standard errors).

every 2 months for 6 months. At every visit, two interviewer-administered instruments were used to assess the effectiveness of the studied combination of agents: the Lesquene index of severity of osteoarthritis of the knee (ISK)²¹ and the visual analog version of the Western Ontario and McMaster Universities osteoarthritis index (WOMAC).²³ The primary outcome was the ISK because it was used by most of the previous studies on glucosamine or chondroitin sulfate. The same interviewer was used for all patients and for every visit. Patients were examined by the principal investigator at every visit. At each visit, patients were asked to make a global self-assessment of their OA on a visual analog scale. When administering ISK, WOMAC, and patient's global assessment, patients were instructed to consider their condition over the previous 2 weeks (vs how they felt on the day of the examination).^{21,23} A daily diary of patients' use of rescue pain medications was kept by the patient. They were allowed to use over-the-counter NSAIDs and acetaminophen. Use of rescue medication greater than 3 days per week was discouraged. Information was also collected on the rate, duration and severity of adverse events.

The study was approved by the Margaret R. Pardee Memorial Hospital Institutional Review Board and was conducted in accordance with the World Medical Association's Helsinki Declaration of 1975, as revised in 1983. An informed consent containing details of the study was provided to patients prior to enrollment. All patients' information was kept confidential.

Statistical analysis

The sample size was calculated to achieve a study power of 80%. This was based on a difference of two points or more between the intervention and placebo in the primary outcome (ISK score), with a standard deviation of 3.0 or less. The WOMAC score was collected as a secondary outcome for comparative purposes. Missing data for patients were imputed using the data of the last recorded visit as a conservative estimate. The 'intention-to-treat' concept was implemented. In other words, persons assigned to either intervention or placebo groups were

analysed as such irrespective of their compliance. All patients that had a baseline visit and received their medications were included in the analysis.

Several characteristics of the patient population were analysed. A statistical comparison of these characteristics was carried out to verify the comparability of the intervention and the placebo groups. These characteristics are listed in Table I. Repeated measurement analysis was done using SAS[®] (Statistical Analysis System, Cary, NC), PROC MIXED[®]. We employed a linear model with fixed effect terms for baseline score, treatment group, time and the group by time interaction. As part of the analysis, we computed differences between treatment groups at 2 months, 4 months and 6 months, adjusting for any baseline differences, and tested the significance between groups. Due to the heterogeneity of variances among time points, an unspecified covariance structure was used throughout. All P-values reflect between-group comparison. Analysis was planned *a priori* to be stratified by the radiographic severity of OA, with the mild/moderate severity as the primary study population.

Other data in the form of counts were statistically analysed using chi-square tests for contingency tables. A positive response to the studied compounds was defined as improvement of 25% or more in the various parameters studied (ISK, WOMAC or patients global assessment). Quantitative data, for baseline differences, were analysed using two-sample t-test. Pearson correlation coefficient was calculated to test the association between the changes in the ISK score, the WOMAC score, and the patient's global assessment. Dr Murray Selwyn, with the 'Statistics Unlimited, Inc.', performed the primary statistical analysis and no interim analysis was scheduled.

Results

Demographics and characteristics of study patients at baseline are presented in Table I, showing no significant difference between the placebo and the intervention groups, verifying the comparability of the two groups.

Among the 93 patients, 72 (77%) had radiographically mild or moderate OA (Kellgren and Lawrence radiographic

Table II
Mean (\pm standard error) and percent change from baseline of clinical findings over the study period among study patients stratified by radiographic severity

	Visit	Mild/moderate cases (N=72)		Severe cases (N=21)	
		Placebo (N=39)	Intervention (N=33)	Placebo (N=8)	Intervention (N=13)
Lequesne ISK	Baseline	10.4 (\pm 0.4)	10.2 (\pm 0.4)	10.7 (\pm 1.2)	11.1 (\pm 0.8)
	At 2 months	9.6 (\pm 0.5)	8.9 (\pm 0.5)	10.1 (\pm 1.4)	10.2 (\pm 0.8)
	At 4 months	9.2 (\pm 0.6)	7.2 (\pm 0.6)*	9.6 (\pm 1.5)	9.4 (\pm 0.9)
	At 6 months	9.0 (\pm 0.6)	7.4 (\pm 0.6)†	9.9 (\pm 1.6)	9.6 (\pm 1.0)
	\geq 25% improvement	11 (28%)	17 (52%)‡	2 (25%)	3 (23%)
WOMAC	Baseline	944 (\pm 55)	908 (\pm 71)	1089 (\pm 158)	1187 (\pm 119)
	At 2 months	831 (\pm 64)	768 (\pm 71)	984 (\pm 166)	1134 (\pm 121)
	At 4 months	774 (\pm 79)	655 (\pm 72)	900 (\pm 174)	1041 (\pm 126)
	At 6 months	724 (\pm 87)	626 (\pm 77)	882 (\pm 183)	1033 (\pm 126)
	\geq 25% improvement	16 (41%)	19 (58%)	2 (25%)	4 (31%)
Patient's global Assessment	Baseline	49.4 (\pm 3.4)	48.9 (\pm 4.0)	60.4 (\pm 6.6)	54.0 (\pm 3.9)
	At 2 months	40.5 (\pm 3.4)	39.0 (\pm 3.7)	53.0 (\pm 5.5)	50.1 (\pm 4.5)
	At 4 months	38.4 (\pm 4.0)	31.4 (\pm 3.8)	47.4 (\pm 5.9)	46.5 (\pm 5.1)
	At 6 months	36.1 (\pm 4.5)	30.8 (\pm 4.1)	43.9 (\pm 8.2)	45.2 (\pm 4.9)
	\geq 25% improvement	18 (46%)	23 (70%)§	3 (38%)	4 (31%)

* $P=0.003$, † $P=0.04$, ‡ $P=0.04$, § $P=0.04$. These P values represent the significant differences between the changes in the intervention and the control groups.

grades 2 and 3) and 21 (23%) had severe OA (grade 4). The results are presented in Table II. The ISK in the radiographically mild or moderate group was 10.4 (\pm 0.4) in patients receiving placebo at baseline and 10.2 (\pm 0.4) in patients receiving the intervention. By 4 months the ISK had dropped to only 9.2 (\pm 0.6) in the placebo group but went down to 7.2 (\pm 0.6) in the intervention group. The difference in the ISK was highly significant ($P=0.003$). At six months the difference in the ISK of the mild or moderate placebo group vs the intervention group was also significant ($P=0.04$). A significant difference was not noted at two months ($P=0.2$). Although a similar trend of improvement was observed, the results were not significant when measured by the WOMAC score ($P=0.5$) or by the patient's global assessment ($P=0.4$). The Pearson correlation coefficients (R) between the changes in OA symptoms measured by various instruments were as follows: ISK/WOMAC $R=0.56$, $P=0.001$; ISK/global patient's assessment $R=0.36$, $P=0.0003$; and WOMAC/global patient's assessment $R=0.63$, $P=0.0001$.

For purposes of this study, response to the treatment was defined as a 25% improvement in the parameter studied (ISK, WOMAC or patient's global assessment), with the ISK as the primary outcome. The results are presented in Table II. In the radiographically mild/moderate subgroup of patients, the ISK showed that 52% of the intervention group responded vs 28% of the placebo group ($P=0.04$). When the WOMAC was used to evaluate the results 58% of the intervention group responded vs 41% of the placebo group ($P=0.2$). When the patients' global assessments were used to evaluate the results 70% of the intervention group responded vs 46% of the placebo group ($P=0.04$).

With the numbers available ($N=21$), there were no significant differences in the response of the intervention vs placebo groups of patients with radiographically severe arthritis whether the results were measured with the ISK, WOMAC or patients' global assessments.

The drop in the use of rescue pain medications, from two months in the study to six months, by 50% or more, approached but did not achieve significance in the

mild/moderate subgroup (19% and 39% in the placebo and intervention groups, respectively, $P=0.08$). It also approached but did not achieve significance in the severe subgroup (0% and 31% in the placebo and intervention groups, respectively, $P=0.1$).

Adverse events are presented in Table III. There was a 19% incidence of adverse events among the placebo group and a 17% incidence of adverse events among the intervention group. The majority of these events were transient. One patient dropped out in both the placebo and intervention groups because of gastrointestinal upset. Another patient in the placebo group dropped out for knee joint replacement surgery. A third patient in the placebo group dropped out because of intolerable pain requiring intra-articular steroid injection. Thus, only four patients (4%) dropped out of the study.

Reasons for missing data were as follows (out of 372 total visits): major change in physical activities (one visit, 0.3%), 50% or more of the follow-up period taking pain medications (three visits, 0.8%), patients dropped out (nine visits, 2.4%), co-morbidity not related to the study medication and accidents (six visits, 1.6%), steroid administration (12 visits, 3.2%), study termination (seven visits,

Table III
Adverse events in the placebo and the intervention groups

Events	Placebo (N=47)	Intervention (N=46)
GI upset (constipation, indigestion, gas)	10 (21%)	7 (15%)
Bad taste	3 (6%)	1 (2%)
Fatigue	—	1 (2%)
Diabetes (type II)	—	1 (2%)
Hypothyroidism	—	1 (2%)
Muscle cramps	1 (2%)	—
Phlebitis	1 (2%)	—
Total number of patients*	9 (19%)	8 (17%)

*The total number of patients does not match the numbers mentioned in the individual cells in the table because some patients reported more than one adverse event.

1.9%), unacceptable time lapse between visits (24, 6.5%). Acceptable time limits were 49–77 days between visits or a total study period of 147–210 days. Thus, 16.6% (62/372) of the data was modified as described under statistical analysis.

Discussion

We presented the first clinical trial of the combination of glucosamine hydrochloride, sodium chondroitin sulfate and manganese ascorbate in the management of knee OA. In this study a significant improvement in OA symptoms was observed. The results are in agreement with previous reports on osteoarthritic animals^{49–52} and humans⁶² studying the same combination of glucosamine, chondroitin sulfate and manganese ascorbate. In one of these studies, Leffler *et al.*⁶¹ studied middle-aged athletic population suffering from knee and back OA and reported significant symptomatic improvement.

Most of the studies of either glucosamine or chondroitin sulfate have used the ISK score as their primary outcome showing similar magnitude of improvement to the current study. According to Lequesne *et al.*,⁵³ it is expected in the assessment of a new intervention to find an initial score of 8–12 points by ISK score and to find an average decrease of three points after starting the intervention. The fact that patients in the radiographically severe group did not improve, with the available number, is not surprising since the proposed mechanism of action is dependent on the existence of cartilage in the arthritic joint. Most previous clinical trials on the individual agents did not include, or did not report separately, this group of patients in their study population. It is worthwhile to note that there are a small number of patients in the radiographically severe group in our study. Thus, a definitive statement regarding the efficacy in this group of patients cannot be made.

Although the efficacy in the mild to moderate group was significant as reflected in the change of the ISK score, the WOMAC score did not achieve statistical significance. We used the visual analog version of the WOMAC index. It is possible that in the case of studies spanning several months, using agents that exhibit subtle improvement might result in more variability because patients have more difficulty deciding on the level of their symptoms with the visual analog. To the authors' knowledge, the only published study that used WOMAC index in assessing a slow acting agent in the treatment of OA was by Hout *et al.*⁶⁸ Despite a positive trend, the results were not statistically significant because of the high variation in the WOMAC index.

The correlations between the ISK and WOMAC scores were 'statistically' significant. Nevertheless, the correlation coefficients are not impressively high, which is in concordance with a previous report by Bellamy *et al.*²³ Notice also that the correlation between the change in WOMAC score and patient's global assessment is higher than between either of them and the change in the ISK score, which might be a function of the order of administration of questionnaires. A comprehensive assessment of validity has been reported for both the ISK and the WOMAC scores. However, they were introduced with different specific concepts of measurement.²⁰ The limited accordance of ISK and WOMAC scores should not be regarded as evidence against their usefulness in clinical studies, but as an indication that these two scores measure slightly different aspects of the same disease. For example, in pain

measurement, the ISK score measures mainly the type of pain while the WOMAC score measures the severity of pain.²⁰

Interestingly, the studied combination contained manganese. The rationale behind its use is that manganese storage in the body is minimal.⁶² However, while dietary manganese overload appears to be non-existent, it is estimated that 37% of the American population has low manganese intake.⁵³ Occult manganese deficiency appears to be a likely factor in bone loss and degenerative joint conditions for even well-fed Americans.⁶⁴ Manganese salts have superoxide dismutase-like activity which is dose related,⁶⁵ and is a co-factor for mitochondrial superoxide dismutase⁶² which inhibits oxidative damage in tissues.⁶⁵ Furthermore, manganese is an essential trace element that has a role in GAG synthesis and in activating glycosyltransferase enzymes that attach modified sugars to proteins (collagen) and to each other.¹⁰ To date, manganese toxicity due excessive dietary intake alone has not been firmly identified in humans.⁶⁶ The level of oral intake of manganese associated with adverse effects is debatable reflecting a number of factors influencing manganese retention, such as past manganese intake and iron, calcium, phosphorus and phytate in the diet.⁶⁷ Nevertheless, caution is warranted in this area and high intake of manganese is not recommended.⁶⁶

With the publicity given to the studied agents, the public at large is extensively self-medicating. Since these substances are available over the counter under a number of different labels, there is unfortunately no guarantee that the quality of glucosamine and chondroitin sulfate they receive is satisfactory. Hungerford⁴⁷ draws attention to the fact that glucosamine and chondroitin sulfate are both obtained from animal tissue sources and purity can vary widely depending on extraction techniques and analysis technology. Most previous studies on glucosamine and chondroitin sulfate, and certainly the current study, were conducted using carefully assayed, purified compounds. The purity and molecular weight of the compounds used can certainly be expected to affect bioavailability and consequently efficacy. Glucosamine and chondroitin sulfate are considered dietary supplements in the U.S.A., rather than drugs. Therefore, the Food and Drug Administration does not regulate their manufacturing. Although many brands of glucosamine and chondroitin sulfate are available over the counter, independent laboratory analyses have shown that many products do not actually contain the amounts or purity claimed on the label.⁴⁸ It would be logical to recommend that manufacturers use self-imposed quality-control programs and pharmaceutical-type good manufacturing practices (GMPs) until the FDA regulates the industry. A similar concern was voiced in a recent editorial in the *New England Journal of Medicine*.⁵⁵

There was no significant difference in the rate of adverse events between the intervention and the placebo groups. One patient in the intervention group was diagnosed with type II diabetes mellitus during the study. Intravenous glucosamine has been shown to result in hyperglycemia in experimental animals.^{56–58} However, these studies loaded the animals with large doses of glucosamine given in a very short period. A safety study of oral administration of the same combination in animals did not report elevation of blood glucose.⁴⁹ Furthermore, no significant elevation in blood glucose was reported by previous clinical trials.^{33,62} The authors did not have baseline blood studies and were

unable to substantiate a causal relation in this case. Further studies are warranted.

Agents such as glucosamine have been proposed in the XVIIIth International League Against Rheumatism (ILAR) Congress of Rheumatology as slow acting agents in OA based on its pharmacological and clinical profile.⁴⁵ Thus, such agents have an entirely different mechanism of action from other available medications. The studied combination of agents has potential for being a disease modifying osteoarthritis drug (DMOAD) based on previous *in vitro*,¹⁵ *in vivo*,⁵⁹⁻⁶¹ and clinical^{16,17} studies. They are postulated to slow the degenerative process of osteoarthritis. As of now, there is no established DMOAD available. DMOADs have the potential to provide yet another tool in the armamentaria against OA, the leading cause of joint replacement. The potential impact of DMOADs on the field of joint replacement is profound. Extending the interval between diagnosis and surgical intervention, thus postponing joint replacement, would be especially beneficial for younger patients facing the possibility of more than one replacement in their lifetime. Our study did not address the question of whether or not these agents are DMOADs. Long-term studies are warranted to further investigate this possibility.

In conclusion, the studied combination* of glucosamide hydrochloride, sodium chondroitin sulfate and manganese ascorbate is effective in the management of osteoarthritis of the knee. They have no known serious side-effects.

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