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The Efficacy and Tolerability of Glucosamine Sulfate in the Treatment of Knee Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

BACKGROUND: Osteoarthritis (OA) is the most common form of arthritis and is often associated with disability and impaired quality of life.

OBJECTIVE: The aim of the study was to assess the efficacy and tolerability of glucosamine sulfate (GS) in the treatment of knee OA.

METHODS: Consecutive outpatients affected by primary monolateral or bilateral knee OA were enrolled in this double-blind, double-dummy, prospective, randomized, placebo-controlled trial. One group received GS 1500 mg QD for 12 weeks, and the other group received placebo QD for 12 weeks. The treatment period was followed by a 12-week treatment-free observation phase. Each patient was examined at baseline and at weeks 4, 8, 12, 16, 20, and 24. The primary efficacy criteria were pain at rest and during movement, assessed on a visual analog scale (VAS) of 0 to 100 mm. The secondary criteria included the Western Ontario and McMaster Universities (WOMAC) index for total pain score (W-TPS), total stiffness score (W-TSS), and total physical function score (W-TPFS). VAS, W-TPS, W-TSS, and W-TPFS were evaluated at baseline and at weeks 4, 8, 12, 16, 20, and 24. Analgesic drug consumption (ie, acetaminophen or NSAIDs) was also assessed.

RESULTS: Patient demographics were similar in the GS and placebo groups. Of 60 randomized patients (30 per group), 56 completed the study (28 treated with GS and 28 who received placebo). Statistically significant improvements in symptomatic knee OA were observed, as measured by differences in resting pain at weeks 8, 12, and 16 (all, $P < 0.05$ vs placebo) and in pain during movement at weeks 12 and 16 (both, $P < 0.05$). W-TPS was lower with GS than placebo at weeks 8, 12, and 16 (all, $P < 0.01$), and at week 20 ($P < 0.05$). W-TSS was also lower with GS than placebo at weeks 8, 12, 16, and 20 (all, $P < 0.05$). W-TPFS was lower with GS than placebo at weeks 8 ($P < 0.05$), 12 ($P < 0.01$), 16 ($P < 0.05$), and 20 ($P < 0.05$). Drug consumption was lower in the GS group than the placebo group at weeks 8, 12, 16, and 20 (all, $P < 0.05$). The incidence of adverse events was 36.7% with GS and 40.0% with placebo.

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CONCLUSIONS: GS 1500 mg QD PO for 12 weeks was associated with statistically significant reductions in pain and improvements in functioning, with decreased analgesic consumption, compared with baseline and placebo in these patients with knee OA. A carryover effect was detected after treatment ended. (*Curr Ther Res Clin Exp*. 2009;70:185–196) © 2009 Excerpta Medica Inc.

KEY WORDS: glucosamine sulfate, knee osteoarthritis, efficacy, carryover effect, tolerability.

INTRODUCTION

Osteoarthritis (OA) is the most frequently encountered condition in rheumatology practice, and its prevalence is rising because of the general population's increasing life span.[1] Current treatment of OA includes both nonpharmacologic and pharmacologic modalities.[2] Pharmacologic therapy has been largely confined to analgesics or NSAIDs or selective cyclooxygenase-2 (COX-2) inhibitors (coxibs). However, the use of NSAIDs is limited by their negative side effects on the gastrointestinal tract and on cartilage metabolism,[3,4] and the use of coxibs is associated with an increase in cardiovascular adverse events (AEs).[5,6] Acetaminophen is better tolerated than NSAIDs and coxibs but does not always provide adequate pain relief.[7,8] Studies have been performed to identify agents able to prevent, delay, or stabilize the pathologic changes that occur in OA joints, thereby limiting disease progression.[9–11] These drugs have been classified as disease-modifying or structure-modifying OA drugs.[12,13] Glucosamine sulfate (GS) is a structure-modifying aminomonosaccharide, acting as a preferred substrate for the biosynthesis of glycosaminoglycan chains and, subsequently, for the production of aggrecan and other proteoglycans of the articular cartilage.[14,15] Moreover, GS stimulates the synthesis of cartilage matrix and inhibits the activity of catabolic enzymes, including metalloproteinases.[16,17] In OA animal models, GS is reported to reduce the severity of cartilage histologic lesions and synovial inflammation.[18] Several GS actions can be explained on the basis of the inhibition of nuclear factor κB activation, induced by interleukin-1β, and, consequently, of the transcription of several genes regulating the synthesis of cytokines, chemokines, adhesion molecules, and enzymes (eg, COX-2, inducible nitric oxide synthase, metalloproteinases); all of these agents are associated with synovial inflammation and cartilage disruption in OA.[19,20]

Several clinical trials of treatments for OA have reported significant symptomatic effects and a positive tolerability profile for GS.[21–25]

The effects of GS are supported by data from 2 long-term (ie, 3-year), randomized, controlled, double-blind studies in patients with knee OA treated with GS 1500 mg QD PO[26,27]; however, more recent studies had dissimilar results.[28,29] The aim of the present study was to prospectively evaluate the efficacy and tolerability of GS, in comparison with placebo, in the treatment of patients with symptomatic knee OA.

PATIENTS AND METHODS

This was a prospective, randomized, double-blind, double-dummy, placebo-controlled trial. The study protocol followed the principles of the Declaration of Helsinki and

was approved by the ethics committee of the University of Siena's hospital. Consecutive outpatients of both sexes who were diagnosed with primary monolateral or bilateral knee OA and met the American Rheumatism Association criteria[30] were enrolled in the study from February to September 2007. The patients were studied at the Department of Internal Medicine of the University of Siena. To be eligible, patients had to be symptomatic for ≥3 months before enrollment and have a radiologic grade between I and III, as measured with the Kellgren-Lawrence method.[31] Exclusion criteria were hematologic disorders, renal disease, liver disease, diabetes mellitus, acute illness, neoplasms, other rheumatic diseases, disabling comorbid conditions that would make it impossible for the patient to visit the research center, pregnancy or nursing, and a body mass index >30 kg/m^2. The exclusion criteria were confirmed clinically and, if necessary, by laboratory and instrumental findings. Patients with grade-IV OA (Kellgren-Lawrence) and those who had had joint lavage, arthroscopy, or treatment with hyaluronic acid or other disease-modifying agents during the previous 6 months, or who had been treated with intra-articular corticosteroids during the past 3 months, were excluded from the study.

Having satisfied the screening criteria and after signing an informed consent form, patients were randomized 1:1 to 2 groups using a computer-generated table of random numbers. One group received GS 1500 mg QD for 12 weeks as sachets of powder for oral solution; the other group received a double-dummy placebo formulation that was identical in look, taste, and smell to the active medication but contained only inactive excipients; this placebo was administered at the same time and for the same duration as the active study drug. Placebo and active drugs were prepared by the laboratory of the Department of Pharmacology Giorgio Segre of the University of Siena. Double-blinding conditions were successfully achieved for all patients. Twelve weeks later, patients discontinued the drug or placebo intake, but remained under clinical observation for the following 12 weeks to evaluate a possible GS carryover effect.

For the duration of the study, it was recommended that patients not modify their therapeutic program (for both drug treatments and physical therapy) unless an AE occurred and required management. In particular, they were instructed to avoid corticosteroids and hyaluronic acid infiltrations, arthroscopic surgery, and joint lavage, and to avoid treatment with disease-modifying OA drugs. These recommendations were verified by anamnesis and clinical evaluation of the patients at each visit. Violation of the protocol was cause for exclusion. For rescue analgesia, patients were allowed acetaminophen 500 mg, diclofenac 150 mg, piroxicam 20 mg, naproxen 750 mg, or aceclofenac 200 mg, all of which were to be used as needed and noted daily in a diary.

All patients underwent general medical evaluation and rheumatologic examination by the same physician before the start of the study. For patients with bilateral OA, the most compromised knee was used as the reference. All demographic, anamnestic, and clinical data were collected using a standardized questionnaire.

Each patient was examined at baseline and at weeks 4, 8, 12, 16, 20, and 24 after randomization. All patients were examined and underwent masked assessment by the same physician at the Department of Internal Medicine. Following the Osteoarthritis Research Society International guidelines,[32] clinical assessments at each examination

included: pain at rest and pain with movement on a visual analog scale (VAS) of 0 to 100 mm, with 0 representing the absence of pain; Western Ontario and McMaster Universities (WOMAC) index for knee OA,[33,34] measured as total pain score (W-TPS), total stiffness score (W-TSS), and total physical function score (W-TPFS); and analgesic or NSAID consumption, reported in a daily diary given to each patient, calculated by daily values for 4 weeks.

All patients underwent the following biochemical analyses at baseline and weeks 4, 8, and 12: erythrocyte sedimentation rate; C-reactive protein; serum glucose levels; creatinine; complete blood count; electrolytes; aspartate and alanine aminotransferases; and urinalysis.

Treatment tolerability was assessed by recording AEs reported by the patients in a daily diary or observed by the physician at each clinic visit. The diary was handed to the investigators at the end of the study, and serious AEs were to be immediately reported; therefore, patients with serious AEs were immediately removed from the trial.

STATISTICAL ANALYSIS

Power analysis ($\alpha = 0.05$; $\beta = 0.80$) determined that a sample size of 20 patients in each group was needed to detect a decrease ≥15, with an SD of 20, in VAS score at week 12 of the study. Thirty patients were enrolled per group to allow for dropouts.

Regarding statistical analysis, response to treatment was analyzed for all patients who entered the randomized trial (intent-to-treat analysis). According to the protocol, the last-observation-carried-forward approach was used for patients who did not complete the study. All parameters of this study were reported as mean (SD) values. For all tests, $P < 0.05$ was considered to be statistically significant. The t or χ^2 test was used to demonstrate the homogeneity of the baseline variables between the 2 groups. To evaluate whether there was any overall effect of GS therapy compared with placebo over time, a 2-way analysis of variance for repeated measures was performed, with the clinical assessments (VAS, W-TPS, W-TSS, W-TPFS, and NSAID/analgesic consumption) as dependent variables and group allocation (GS or placebo) and time (baseline and weeks 4, 8, 12, 16, 20, and 24) as factors. Post hoc analyses were performed with a Bonferroni correction when necessary. The χ^2 test was used to compare percentages of AEs. For all statistical analyses, SAS version 9.0 (SAS Institute Inc., Cary, North Carolina) was used.

RESULTS

Sixty patients satisfied the eligibility criteria and were included in the study (**Figure**). Baseline comparison of the GS and placebo groups showed no statistically significant differences in demographics, clinical characteristics, or radiologic features (**Table I**). No statistically significant differences in NSAID and analgesic intake were noted between groups at baseline (**Table I**). Furthermore, at baseline, all biochemical parameters were in normal ranges for all patients. Two subjects (6.7%) in each group withdrew from the study. In the GS group, 1 patient (3.3%) withdrew because of heartburn that developed 2 weeks after treatment initiation, and another (3.3%) withdrew because of a diffuse itch that developed in the first week of treatment (**Figure**).

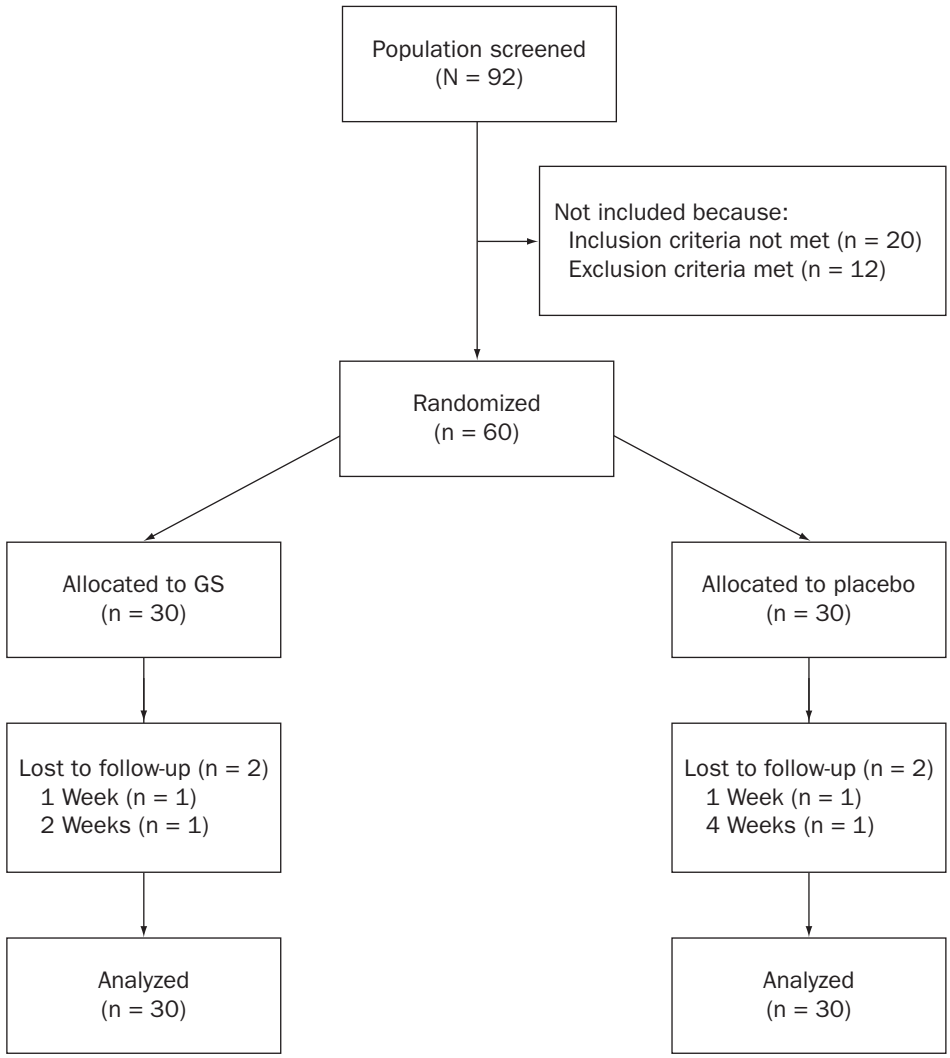

Figure. Flow diagram of a double-blind, double-dummy, prospective, randomized, placebo-controlled trial of glucosamine sulfate (GS) 1500 mg QD PO or placebo QD PO for 12 weeks in patients with osteoarthritis of the knee.

In the placebo group, 1 subject (3.3%) withdrew because of constipation that developed during the first week of treatment, and the other (3.3%) for reported drug ineffectiveness during the fourth week (**Figure**).

Table II compares the differences in the efficacy outcome parameters between patients receiving GS and those receiving placebo. VAS pain scores were significantly lower with GS than placebo during rest at weeks 8, 12, and 16, and during motion at

Table I. Demographic and baseline clinical characteristics of patients with osteoarthritis of the knee who were randomized to receive glucosamine sulfate (GS) 1500 mg QD PO or placebo QD PO for 12 weeks, based on the intent-to-treat analysis (n = 30 in each group).

Variable	GS	Placebo
Age, mean (SD), y	57.2 (7.2)	58.09 (8.3)
Sex, no. (%)		
Female	21 (70.0)	21 (70.0)
Male	9 (30.0)	9 (30.0)
White race, no. (%)	30 (100.0)	30 (100.0)
Body mass index, mean (SD), kg/m^2	22 (7.1)	23 (6.0)
Disease duration, mean (SD), y	6.2 (4.8)	6.4 (4.7)
Kellgren-Lawrence score of disease severity, no. (%)		
I	3 (10.0)	3 (10.0)
II	12 (40.0)	12 (40.0)
III	15 (50.0)	15 (50.0)
Previous NSAID/acetaminophen intake, no. (%)	20 (66.7)	19 (63.3)

weeks 12 and 16 (all, $P < 0.05$). W-TPS was significantly lower with GS than placebo at weeks 8, 12, and 16 (all, $P < 0.01$) and at week 20 ($P < 0.05$). W-TSS was significantly lower with GS than placebo at weeks 8, 12, 16, and 20 (all, $P < 0.05$). W-TPFS was lower with GS than placebo at weeks 8 ($P < 0.05$), 12 ($P < 0.01$), 16 ($P < 0.05$), and 20 ($P < 0.05$). NSAID and analgesic consumption was lower with GS than placebo at weeks 8, 12, 16, and 20 (all, $P < 0.05$).

Regarding VAS, a statistically significant decrease baseline in pain during rest was observed within the GS group at week 8 ($P < 0.05$), weeks 12 and 16 (both, $P < 0.001$), and week 20 ($P < 0.05$) (**Table II**). Moreover, in the GS group, pain during movement decreased significantly from baseline at weeks 12 and 16 (both, $P < 0.05$). With GS, W-TPS and W-TPFS were significantly lower than baseline at weeks 8 (both, $P < 0.05$), 12 (both, $P < 0.001$), 16 (W-TPS, $P < 0.001$; W-TPFS, $P < 0.05$), and 20 (both, $P < 0.05$). W-TSS was significantly lower from baseline at weeks 8, 12, 16, and 20 (all, $P < 0.05$). No statistically significant differences from baseline were observed at any time point for VAS values, W-TPS, W-TPFS, or W-TSS in the placebo group.

NSAID and analgesic consumption decreased in the GS group at weeks 4, 8, 12, and 16 (all, $P < 0.05$). NSAID and analgesic consumption did not change significantly from baseline at any time point in the placebo group (**Table II**).

The rates of the most commonly occurring AEs did not significantly differ between groups. **Table III** shows the type and frequency of the most common AEs that occurred during the treatment period. AEs were reported in 11 patients (36.7%) in the GS group and 12 patients (40.0%) in the placebo group. Two patients (6.7%) receiving GS and 2 patients (6.7%) receiving placebo experienced >1 AE; all of these patients experienced

Table II. Efficacy results in patients with osteoarthritis of the knee who were randomized to receive glucosamine sulfate (GS) 1500 mg QD PO or placebo QD PO for 12 weeks, based on the intent-to-treat analysis (n = 30 in each group). Values are given as mean (SD).

Measure	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Resting pain on VAS							
GS	42.0 (24.2)	38.32 (21.6)	30.01 (20.0)*†	25.4 (19.9)†‡	28.32 (20.9)†‡	33.27 (20.6)*	40.38 (23.2)
Placebo	40.89 (23.6)	41.15 (22.3)	40.53 (21.9)	41.0 (20.5)	41.82 (23.0)	42.00 (21.3)	41.33 (22.3)
Moving pain on VAS							
GS	70.10 (17.3)	68.49 (18.0)	60.03 (18.4)	59.38 (19.3)*†	60.19 (20.0)*†	65.24 (20.8)	70.22 (21.3)
Placebo	71.96 (18.4)	71.58 (19.0)	70.83 (19.0)	70.2 (20.4)	71.33 (19.3)	70.25 (20.0)	71.69 (19.4)
W-TPS							
GS	51.2 (8.3)	48.80 (9.0)	40.32 (10.4)*§	30.56 (11.5)†§	31.85 (12.4)†§	41.22 (13.9)*†	47.75 (14.5)
Placebo	50.03 (6.4)	51.35 (6.8)	52.23 (6.9)	53.3 (7.1)	52.81 (6.7)	51.75 (6.5)	51.05 (6.7)
W-TSS							
GS	49.0 (3.1)	47.81 (3.4)	38.25 (4.0)*†	35.65 (4.1)*†	37.34 (3.8)*†	38.42 (3.9)*†	47.78 (3.3)
Placebo	47.93 (2.3)	46.92 (2.5)	47.08 (3.0)	48.0 (3.3)	48.51 (3.2)	47.53 (3.4)	48.03 (3.3)
W-TPFS							
GS	52.16 (12.3)	47.89 (12.4)	40.85 (12.9)*†	32.82 (13.2)†§	41.21 (14.2)*†	43.11 (13.8)*†	51.85 (12.5)
Placebo	53.94 (14.1)	54.21 (14.4)	54.30 (14.7)	55.1 (14.9)	53.98 (14.2)	54.11 (14.0)	53.27 (14.0)
Daily NSAID/analgesic consumption							
GS	12.10 (3.9)	8.20 (2.8)*	7.80 (2.9)*†	6.60 (3.1)*†	7.65 (2.8)*†	8.30 (2.8)†	9.75 (3.1)
Placebo	11.90 (3.1)	9.80 (2.9)	10.40 (2.8)	10.30 (2.8)	10.85 (2.8)	11.60 (2.9)	12.25 (2.9)

VAS = visual analog scale of 0 to 100 mm; W-TPS = Western Ontario and McMaster Universities (WOMAC) index for total pain score; W-TSS = WOMAC index for total stiffness score; W-TPFS = WOMAC index for total physical function score.

*$P < 0.05$ versus baseline.

†$P < 0.05$ versus placebo.

‡$P < 0.001$ versus baseline.

§$P < 0.01$ versus placebo.

Table III. Type and frequency of adverse events in patients with osteoarthritis of the knee who were randomized to receive glucosamine sulfate (GS) 1500 mg QD PO or placebo QD PO for 12 weeks, based on the intent-to-treat analysis (n = 30 in each group). Data are no. (%).

Adverse Event	GS	Placebo
Any event	11 (36.7)	12 (40.0)
Musculoskeletal pain	5 (16.7)	4 (13.3)
Flu syndrome	2 (6.7)	3 (10.0)
Constipation	2 (6.7)	4 (13.3)
Headache	1 (3.3)	2 (6.7)
Diarrhea	1 (3.3)	1 (3.3)
Itch	1 (3.3)	–
Heartburn	1 (3.3)	–

2 events. Serious AEs occurred in 2 patients (6.7%) from the GS group and 1 patient (3.3%) from the placebo group; therefore, they were withdrawn from the study.

DISCUSSION

The results of this study suggest that GS is associated with statistically significant improvements in symptomatic knee OA as measured by changes in pain, stiffness, and function compared with baseline and placebo. However, the clinical significance of these small changes is not known and requires further research.

Results of previous research suggest that GS, unlike NSAIDs, is not appropriate for short-term analgesia, but is suitable for medium- to long-term management of knee OA, producing global clinical improvements.[22,25,35] The structural effects of the drug on OA were confirmed by our study because most of the reductions in pain and improvements in functioning appeared to persist after therapy ended. In fact, once study treatment was stopped, the symptomatic benefits observed at the end of treatment in the GS group persisted for an additional 6 to 8 weeks, indicating a carryover effect. No published studies on knee OA have described any other molecule with a similar carryover effect. The observed carryover effect may be related to reports that GS stimulates the anabolic activities of cartilage and inhibits the catabolic enzymes and inflammatory mediators that are responsible for articular OA damage.[14–16,19,20]

The reduction in NSAID or analgesic consumption noted in the GS group supports the drug's efficacy. This decrease reached statistical significance at 4 weeks after therapy began, continued for the remainder of treatment duration, and lasted for 8 weeks after treatment cessation.

Our results are not consistent with those of the recent multicenter, double-blind, placebo- and active-controlled Glucosamine/chondroitin Arthritis Intervention Trial

(GAIT)[28] for the treatment of pain in 1583 patients randomly assigned to receive 1500 mg of glucosamine daily, 1200 mg of chondroitin sulfate daily, both glucosamine and chondroitin sulfate, 200 mg of celecoxib daily, or placebo for 24 weeks. In GAIT, the primary outcome measure was a 20% decrease in knee pain from baseline to week 24. The glucosamine hydrochloride 500 mg TID failed to show a significant difference in efficacy versus placebo over a 6-month treatment period. However, glucosamine hydrochloride produces glucosamine plasma levels at least 3 times lower than those achieved by GS 1500 mg QD[36–38]; therefore, its pharmacologic effects may be reduced. Furthermore, sulfates may play a role in the mechanism of action of glucosamine.[39] Regarding the recent study by Rozendaal et al,[29] we believe that it is not possible to apply their conclusions to other settings (such as the present trial) because their study evaluated GS efficacy in 222 patients affected by hip OA who underwent 2 years of treatment with 1500 mg of oral glucosamine sulfate or placebo once daily. Future research should study the efficacy of GS in systemic OA.

GS treatment was well tolerated in this study. The type and frequency of AEs were similar between the GS and placebo groups, and they were generally of minor clinical significance. Only 2 patients (6.7%) in the GS group and 1 patient (3.3%) in the placebo group experienced serious AEs (heartburn and itch in the GS group, and constipation in the placebo group) that resulted in their withdrawal from the study. Routine laboratory parameters remained within normal ranges during GS treatment, supporting the tolerability profile of this agent. In particular, glucose serum levels remained within normal limits, contradicting a previous report that GS increased insulin resistance.[40]

This study had a number of limitations: the duration of the study was short, the sample was small, and the inclusion of patients with knee OA alone was insufficient to determine whether GS could be useful in the treatment of systemic OA. Furthermore, our patients had relatively mild knee pain at baseline, compared with that in classic studies of OA, in which a criterion for enrollment was a disease flare after the discontinuation of NSAIDs.[41,42] However, only patients with moderate to severe pain were treated with GS or other chondroprotective agents in those studies.

CONCLUSIONS

GS 1500 mg QD PO for 12 weeks was associated with statistically significant reductions in pain and improvements in functioning, with decreased analgesic consumption, compared with baseline and placebo in these patients with knee OA. A carryover effect was detected after treatment ended.

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