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Open-Label, Randomized, Controlled Pilot Study of the Effects of a Glucosamine Complex on Low Back Pain

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ABSTRACT

Background: A series of studies has suggested some efficacy of glucosamine in arthrosis of the knee, but virtually no documentation exists regarding its effects on low back pain.

Objectives: The primary objective of this study was to examine whether a 12-week course of a glucosamine complex (GC) could benefit patients having low back pain despite a course of noninvasive physical therapy. In addition, we sought to delineate the subgroup of responders.

Methods: This open-label, randomized, controlled study was conducted at the Division of Rheumatology and Physical Medicine, Erasme University Hospital, Brussels, Belgium. Male and female outpatients aged 40 to 80 years with low back pain (duration, ≥12 weeks; pain score on 10-cm visual analog scale [VAS] [0 = none to 10 = worst imaginable], ≥3 cm) despite noninvasive physical therapy (massage, stretching, heat application, and analgesics for >4 weeks) were included. Patients were randomly assigned to receive, in addition to conventional treatment (CT) (physical therapy plus analgesics/anti-inflammatories), a GC (enriched with sulfonyl methane, silicon, and a botanical extract of *Ribes nigrum*) or CT alone (control) for 12 weeks. Pain at rest and on movement (effort) and early morning lumbar stiffness were measured every 4 weeks using the VAS. The primary end point was improvement in VAS score for pain at rest at 12 weeks. Two validated questionnaires were used to assess improvements in quality of life (QOL) (Oswestry Disability Questionnaire [ODQ] [10 items; scale: 0 = no disability to 60 = maximal disability] and Roland-Morris Disability Questionnaire [RMDQ] [24 items; scale: 0 = no disability to 24 = severe disability]). *Responders* were defined as patients who positively assessed the efficacy of the GC. At each visit, patients were also asked about possible adverse events.

Results: Of 36 enrolled patients, 32 completed the study (18 men, 14 women; mean [SE] age, 64 [2] years; 17 in the GC group and 15 in the control group). Four patients were lost to follow-up. At week 4, changes from baseline VAS scores

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for pain at rest and lumbar stiffness were significantly greater in the GC group compared with the control group ($P < 0.001$ and $P = 0.011$, respectively). At week 4, QOL was found to be improved, as measured using the ODQ, in the GC group compared with the control group ($P = 0.028$), but the between-group difference as measured using the RMDQ was not significant. The improvements from baseline on the questionnaires were sustained over the 12-week period in the GC group (all, $P < 0.001$). Gastrointestinal adverse effects were reported by 1 GC-treated patient and 1 patient in the control group, but neither patient withdrew from the study. Of the 17 GC-treated patients, 9 considered themselves responders, but the profile of a *responder* could not be delineated.

Conclusions: In this study in patients with low back pain, analgesic effect and improvement in QOL were found with the use of GC. GC was well tolerated. (*Curr Ther Res Clin Exp.* 2005;66:511–521) Copyright © 2005 Excerpta Medica, Inc.

Key words: arthrosis, back pain, glucosamine, methylsulfonylmethane, silicon, *Ribes nigrum*.

INTRODUCTION

A series of studies support the efficacy of glucosamine in patients with arthrosis of the knee, with *efficacy* being defined as decreased pain and morning lumbar stiffness, increased quality of life (QOL), and ability to walk.[1,2] A meta-analysis of randomized, controlled trials in patients with knee arthrosis found that glucosamine might be well tolerated and effective in delaying the progression of arthrosis and improving symptoms.[3] Based on the results from Poolsup et al,[4] the administration of glucosamine for several years has been associated with increased cartilage thickness. The mode of action of glucosamine is attributed to a direct effect on the chondrocytes and to an anti-inflammatory effect.[2]

Low back pain is a ubiquitous health problem; between 65% and 80% of people worldwide are affected at some point during their lives. Physical therapies, patient education, and drug therapy are the cornerstones of treatment. However, this approach is not sufficiently effective in many patients, especially if the condition is chronic (>12 weeks).[5]

NSAIDs are effective for short-term symptomatic relief in acute episodes of low back pain. However, sufficient evidence for their effects on chronic low back pain is lacking,[6] and to date, there is no consensus or specific guidelines for the management of chronic low back pain.[7] For these reasons, many patients with chronic backache (and other chronic rheumatic conditions) look for other treatments. Accordingly, about half of rheumatology patients use complementary and/or alternative medicine, including nutraceuticals and phyto-anti-inflammatory drugs.[8] A substantial evidence base is beginning to emerge for the efficacy of a few nutraceuticals and medicinal plants in the treatment of musculoskeletal disease, notably glucosamine, adenosyl methionine, silicon, and *Ribes nigrum* (black currant), with data suggestive of potential chondropro-

tective, anti-inflammatory, anti-metalloproteasic, anti–cyclooxygenase-2, and bone-protective activities.[8–16]

In this study, we used a commercially available glucosamine complex (GC) containing glucosamine sulfate 750 mg, enriched with 100 mg of a botanical extract of *Ribes nigrum*, containing flavonoids, phenols, and prodelphinidins, with anti-inflammatory properties. It was also enriched with methylsulfonylmethane 1000 mg (a sulfur found in fruits and vegetables and thought to possess analgesic effects in degenerative rheumatisms[12]) and colloidal silicon 50 mg (associated with increased trabecular bone volume[9–13,16]). For osteoarthritis, the recommended dosage of this GC is 2 powder sachets per day for at least 12 weeks.[17]

The majority of the studies showing clinical benefit of glucosamine have focused on arthrosis of the knee, hip, or thumb,[2] but based on a literature search using MEDLINE (key terms: *glucosamine* and *low back pain*; years: 1965–2005), no studies in patients with painful common lumbar arthrosis have been published, even though all of these disorders are of degenerative origin, are linked to the mechanical nature of the pain, and share a similar therapeutic approach.[1–3]

Therefore, the aim of this study was to determine whether the addition of GC BID for 12 weeks to a regimen of conventional treatment (CT) would clinically benefit patients with common chronic low back pain and arthrosis.

PATIENTS AND METHODS

This randomized, open-label, controlled pilot study was conducted at the Division of Rheumatology and Physical Medicine, Erasme University Hospital, Brussels, Belgium.

Inclusion and Exclusion Criteria

Male and female patients between 40 and 80 years of age were recruited from a group of consecutive outpatients referred between January and April 2004 for the treatment of chronic low back pain with associated signs of lumbar arthrosis on radiography (eg, uni- or multilevel intervertebral disc space narrowing, condensation of the vertebral plateaus, osteophytosis, degenerative changes of the interapophyseal joint). To be eligible for the study, patients had to have been receiving stable treatment with analgesic/anti-inflammatory drugs and standard physical rehabilitation, including massage, stretching, and heat application, twice weekly for at least 4 weeks, without sufficient clinical improvement (pain score ≥3 on a 10-cm visual analog scale [VAS] [0 = no pain to 10 = worst possible pain]). All patients were undergoing monthly consultations at the clinic.

Patients were excluded if they had any known cause of low back pain other than lumbar arthrosis (eg, osteoporosis, spondyloarthropathy, metastasis, Paget's disease) or any factor that could interfere with the efficacy assessment (eg, de-

pression, anxiety, fibromyalgia, gastrointestinal disturbance). This information was obtained from patients' medical files and during the inclusion visit.

This pilot study used questionnaires concerning a neutraceutical (not registered as a drug but as a food supplement), and was performed before the 2004 publication of the new Legislation on Experimentation concerning experiments on humans (following the European Directive). Thus, the protocol was not submitted to an ethics committee for approval. Nonetheless, prior to inclusion, patients were informed of the aim of the study, the characteristics of the GC, and the benefits and risks expected from the administration of the GC and from continuing with their CT regimen; each patient's oral informed consent was obtained.

Treatment

Patients' CT regimens (anti-inflammatory and physical therapy) were to remain stable throughout the study period. Patients were selected randomly by means of a randomization table by Pocock[16] to receive GC (2 powder sachets per day [with meals]) or CT alone (control group) for 12 weeks. Patients agreed to be reevaluated during their monthly consultations. Neither the investigators nor the patients were blinded to treatment assignment.

Efficacy Assessments

To assess the level of clinical benefit, we used clinical parameters (VAS scores for pain and lumbar stiffness and 2 QOL questionnaires).

Intensity of Lumbar Pain and Stiffness

Patients were asked to rate their pain at rest, pain on movement, and lumbar stiffness in the past 24 hours on the VAS.

Quality of Life

To assess QOL, measured as function in performing activities of daily living, patients were asked to complete (in the absence of the physician) the validated Oswestry Disability Questionnaire (ODQ)[16,18–20] and Roland-Morris Disability Questionnaire (RMDQ).[18,19] The 10-item ODQ[16,18,19] takes into account and quantifies incapability of movement while the patient washes and dresses, carries weights, walks, and sits or stands up; quality of sleep and social life; traveling comfort; and the evolution of the pain (scale: 0 = no disability to 60 = maximal disability). The RMDQ[18,19] is another QOL questionnaire with 24 items that does not note the severity of each item but mainly focuses on *yes* or *no* responses about positions and situations causing lumbalgia (eg, when remaining seated, walking, getting up, bending over, getting dressed) (scale: 0 = no disability to 24 = severe disability).

Patient Global Assessment

At the end of the study, patients were asked to provide a global assessment of the treatment they received (ie, "Were you satisfied?"; possible answers: yes [pos-

itive] or no [negative]),[18,21] and whether they believed they could discontinue their regular consumption of analgesic/anti-inflammatory drugs. *Responders* were defined as patients who positively assessed the efficacy of the GC.

Tolerability and Compliance Assessments

At each clinic visit, patients were interviewed concerning any undesirable effects (especially pyrosis, nausea, abdominal cramps, diarrhea, rash, fatigue, malaise, and any other adverse event), and about their compliance with the treatment regimen.

Statistical Analysis

A per-protocol analysis (without prior power analysis for determining sample size) was used.[22] The normality of the variable distribution was verified using the Shapiro-Wilks test. The statistical analysis consisted of an analysis of variance (ANOVA) of 2 factors (groups and periods of time) with frequent measuring of the periods of time and the interaction time with the group. Although the F ratio on ANOVA was found to be significant, we compared the means using a modified *t* test for paired data. Baseline demographic and clinical characteristics were compared between the 2 treatment groups and the 2 subgroups (responders vs nonresponders) using the Student *t* test for independent measures. The threshold $P < 0.05$ was considered statistically significant. The results are expressed as mean (SE).[22] SPSS version 2 (SPSS Inc., Chicago, Illinois) was used in the calculations.

RESULTS

Patient Population

Thirty-six patients were enrolled in the study. Four patients (1 in the glucosamine group and 3 in the control group) were lost to follow-up and were not included in the intent-to-treat analysis; the remaining 32 patients completed the study and were included in the safety analysis (18 men, 14 women; mean [SE] age, 64 [2] years; GC group, 17 patients; control group, 15 patients). No significant differences in male/female ratio, age, duration of low back pain, or concomitant use of anti-inflammatory/analgesic drugs were found between the 2 groups (**Table I**).

Efficacy

Pain at Rest

In the GC group, the VAS score was significantly improved from baseline at 4, 8, and 12 weeks (all, $P < 0.001$). At 4 weeks of treatment, the mean change from baseline in VAS score for pain at rest was significantly greater in the group of patients treated with the GC compared with that in the control group (–2.18 vs +0.13; $P < 0.001$). This difference continued at weeks 8 and 12 (both, $P < 0.01$) (mean VAS changes at 12 weeks, –4.06 in the GC group vs –1.46 in the control

Table I. Demographic and baseline clinical characteristics of the study patients.*

Characteristic	GC (n = 17)	Control (n = 15)
Age, mean (SE), y	67 (3)	62 (4)
Sex, no.		
Male	10	8
Female	7	7
Duration of back pain, mean (SE), y	9.8 (2.4)	7.8 (2.0)

GC = glucosamine complex.
*No significant between-group differences were found.

group). Throughout the 12-week treatment period, the mean VAS score for pain at rest was statistically similar to that at baseline in the control group (**Table II**).

Pain on Movement

The mean (SE) VAS score for pain on movement in the GC group was significantly lower at 4 weeks compared with baseline (3.60 [0.73] vs 6.17 [0.38]; $P < 0.001$); the differences at weeks 8 and 12 were nonsignificant. In the control group, the mean (SE) VAS score was significantly improved at week 8 compared with baseline (3.71 [1.14] vs 6.07 [0.59]; $P < 0.002$); the differences at weeks 4 and 12 were nonsignificant. The between-group difference in mean (SE) VAS scores for pain on movement was significant only at week 12 (2.08 [0.60] in the GC group vs 4.00 [1.39] in the control group; $P = 0.029$) (**Table II**).

Lumbar Stiffness

Although the mean (SE) VAS score for lumbar stiffness was significantly improved from baseline at weeks 4 and 12 in the patients treated with GC (3.57 [0.89] at week 4 and 1.01 [0.39] at week 12 vs 5.94 [0.81] at baseline; $P < 0.008$ and $P = 0.011$, respectively), this improvement was not observed at any time point in the control group. The improvement in the GC group was significantly greater compared with that in the control group at week 12 ($P = 0.011$) (**Table II**).

Quality of Life

Oswestry Disability Questionnaire

The mean score on the ODQ[16,18–20] was significantly improved from baseline at weeks 4, 8, and 12 in the GC group (all, $P < 0.001$) (**Table II**). In the control group, the score was not improved from baseline until week 12 ($P < 0.001$). At the end of the 12-week study, a significant difference in ODQ score between the 2 groups was observed ($P = 0.028$).

Table II. Clinical parameters over 12 weeks of administration of glucosamine complex (GC) (n = 17) or placebo (control) (n = 15) in patients with chronic low back pain (N = 32). Values are mean (SE) unless otherwise noted.

Parameter	0 Weeks (Baseline)	4 Weeks	8 Weeks	12 Weeks
Score for pain at rest[a]				
GC	4.65 (0.69)	2.47 (0.72)[b,c]	1.78 (0.87)[b,c]	0.59 (0.33)[b,d]
Control	3.47 (0.57)	3.60 (1.03)	3.75 (0.94)	2.01 (1.18)
Score for pain on movement[a]				
GC	6.17 (0.38)	3.60 (0.73)[b]	2.38 (0.68)	2.08 (0.60)[e]
Control	6.07 (0.59)	5.40 (1.83)	3.71 (1.14)[f]	4.00 (1.39)
Score for lumbar stiffness[a]				
GC	5.94 (0.81)	3.57 (0.89)[g]	3.56 (1.34)	1.01 (0.39)[h,i]
Control	4.13 (0.89)	2.86 (0.86)	2.00 (1.08)	2.63 (0.98)
QOL score (ODQ[j])				
GC	30.05 (1.80)	23.82 (2.56)[b]	22.22 (2.20)[b]	18.69 (1.94)[b,k]
Control	25.80 (2.28)	21.00 (2.89)	23.71 (3.96)	18.00 (4.17)[b]
QOL score (RMDQ[l])				
GC	9.76 (1.09)	6.80 (1.52)[b]	5.67 (1.65)[b]	5.38 (1.20)[b]
Control	7.86 (1.23)	4.75 (2.17)[b]	6.71 (1.49)[b]	4.57 (1.68)[b]
Anti-inflammatory/ analgesic use, no.				
GC	7	2	2	2
Control	8	6	6	6

QOL = quality of life; ODQ = Oswestry Disability Questionnaire[16,18–20]; RMDQ = Roland-Morris Disability Questionnaire.[18,19]

[a] 10-cm visual analog scale: 0 = none to 10 = worst possible.

[b] $P < 0.001$ versus baseline.

[c] $P < 0.001$ versus control group.

[d] $P < 0.01$ versus control group.

[e] $P = 0.029$ versus control group.

[f] $P < 0.002$ versus baseline.

[g] $P < 0.008$ versus baseline.

[h] $P = 0.011$ versus control group.

[i] $P = 0.011$ versus baseline.

[j] ODQ scale[16,18–20]: 0 = no disability to 60 = maximal disability.

[k] $P = 0.028$ versus control group.

[l] RMDQ scale[18,19]: 0 = no disability to 24 = severe disability.

Roland-Morris Disability Questionnaire

The mean RMDQ[18,19] scores were significantly improved from baseline at weeks 4, 8, and 12 in both groups (all, $P < 0.001$) (**Table II**), but no significant between-group differences were found.

Patient Global Assessment

After 12 weeks of treatment, 8 of 17 patients in the GC group regarded their condition as well improved and were considered responders.

Of the 7 GC-treated patients receiving anti-inflammatory/analgesic drugs before enrollment, 5 were able to spontaneously discontinue their anti-inflammatory/analgesic drug use within the first 4 weeks, whereas of the 8 patients receiving anti-inflammatory/analgesic drugs before enrollment in the control group, 2 discontinued use ($P < 0.001$).

Responders

In the subanalysis of patients in the GC group classified as *responders* (8 patients) or nonresponders (9), the clinical parameters (age, sex, duration of symptoms, pain on rest and movement, intensity of lumbar stiffness, and the ODQ and RMDQ scores) were statistically similar between the 2 subgroups (**Table III**).

Tolerability

Abdominal discomfort (gastralgia) was reported at 8 weeks by 1 patient in the GC group and by 1 patient in the control group. No other adverse events were reported. None of the patients discontinued treatment due to an adverse event.

Table III. Characteristics of responders* and nonresponders to 12 weeks of administration of glucosamine complex (GC) in patients with chronic low back pain. Values are mean (SE).

Characteristic	Responders (n = 8)	Nonresponders (n = 9)	*P*
Age, y	71 (8)	63 (15)	0.18
Duration of lumbar pain, y	9 (13)	8 (6)	0.81
Score for pain at rest†	5.44 (2.55)	3.75 (3.10)	0.23
Score for pain on movement†	6.11 (0.92)	6.25 (2.12)	0.87
Score for lumbar stiffness†	6.55 (3.35)	5.25 (3.45)	0.44
QOL score (ODQ‡)	32.55 (7.90)	27.25 (6.13)	0.14
QOL score (RMDQ§)	10.88 (4.13)	8.50 (4.84)	0.28

QOL = quality of life; ODQ = Oswestry Disability Questionnaire[16,18–20]; RMDQ = Roland-Morris Disability Questionnaire.[18,19]

* *Responders* were defined as patients who positively assessed the efficacy of the GC.

† 10-cm visual analog scale: 0 = none to 10 = worst possible.

‡ ODQ scale[16,18–20]: 0 = no disability to 60 = maximal disability.

§ RMDQ scale[18,19]: 0 = no disability to 24 = severe disability.

DISCUSSION

The results of this preliminary study suggest that adding the GC to the CT regimen for chronic low back pain contributes to faster and more significant improvements in pain at rest, pain on movement, and lumbar stiffness (as measured using pain and stiffness scales), and QOL (as measured using QOL questionnaires) compared with CT alone.

Improvement, based on the results of the ODQ,[16,18–20] was found with GC use, but the GC did not add a significant additional benefit based on the results of the RMDQ.[18,19] The lack of a difference found with the RMDQ[18,19] might mean a lack of benefit, or might be the result of a statistical limitation (small number of patients) or a methodologic limitation (lack of sensitivity of the RMDQ for chronic low back pain) to objectify an additional benefit.

The mode of action of the GC remains unclear. It contains glucosamine, natural sulfur, an extract of *Ribes nigrum,* and silicon. Although this group of compounds is used for the treatment of rheumatic pain, the precise role of each component has not been identified.[10–15] However, a hypothesis concerning the mode of action of the GC can be proposed based on the results of the present study. First, the slowness of the improvement (4 weeks vs a few hours or days with central or medullary analgesic effect)[5] and the fact that the lumbar anatomic structures have little cartilage (compared with those in the knee)[5] render a chondroprotective effect unlikely. A slow anti-inflammatory or analgesic mode of action is more likely based on the data. The benefit could be due to the individual components in the GC or their combination. The treatment also was found to work on different pain parameters and might provide clinical benefit in addition to that of CT (based on rehabilitation techniques with suppleness and analgesic effects).

Based on the literature search, these data, if confirmed, are virtually the first to suggest that glucosamine alone or in combination with additional components could be associated with an analgesic/anti-inflammatory benefit in patients with low back pain, a condition not included to date as a goal of the potential development of GC. The circumferences of the lumbar disks and the interapophyseal caps are innervated by delicate fibers that can become the center of a slower, neurogenic inflammatory process, causing the release of neurogenic mediators (eg, substance P, *calcitonin gene*–related peptide) and non-neurogenic mediators (eg, serotonin, histamine), and that could be a potential target of the GC.[5,21,23]

Study Limitations

Interpretation of the present data is difficult because of the small number of patients, the lack of a control group, and the open-label design.

The number of patients in this study was limited. It cannot be ruled out that the patients initially experienced different evolved types of chronic low back pain and that these distinctions are difficult to resolve with this small number of participants.

The GC was well tolerated with the exception of gastralgia reported in 1 patient. However, this adverse effect might have been caused by the analgesic/

anti-inflammatory treatment instead of the GC, because gastralgia also occurred in 1 patient who was not receiving GC. In addition, the symptom did not necessitate interruption of the treatment.

Because this was an open-label pilot study, methodologic bias cannot be ruled out, especially because the study contained subjective assessments (eg, quantification of pain and stiffness). Nonetheless, the study employed commonly used questionnaires such as the ODQ,[16,18–20] which can measure disability due to pain more objectively compared with patient or clinician global assessment.

Because low back pain can improve spontaneously, a placebo effect may have occurred. However, the placebo effect is generally time limited,[2,5–7] whereas the improvement associated with the GC continued through week 12 of treatment, with most of the differences being statistically significant. If the present data are confirmed, the GC could be of potential benefit in low back pain.

The original composition of this GC did not allow extrapolation of these results with regard to lumbalgia to other "chondroprotector" substances with glucosamine alone or its derivatives. If these findings were confirmed, this GC might find a place in the treatment of chronic low back pain.

CONCLUSIONS

In this study in patients with chronic low back pain, analgesic effect and improvement in QOL were found with the use of glucosamine sulfate complex. The study drug was well tolerated.

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