

Effect of Glucosamine on Pain-Related Disability in Patients With Chronic Low Back Pain and Degenerative Lumbar Osteoarthritis

A Randomized Controlled Trial

Philip Wilkens, MChiro

Inger B. Scheel, PhD

Oliver Grundnes, PhD

Christian Hellum, MD

Kjersti Storheim, PhD

OSTEARTHRTIS (OA) IS A common condition that currently affects more than 20 million individuals in the United States, and this number is expected to increase.¹ Like the peripheral joints, the spine demonstrates osteoarthritic (facet joint changes) and degenerative alterations (disk area changes).² These findings are often present independently of low back pain (LBP).³ Nevertheless, studies indicate that such findings may cause LBP.²

Low back pain is widespread and is the second most common concern expressed by patients in primary care.³ It poses a diagnostic and therapeutic challenge to clinicians due to the unclear etiology and the range of interventions with limited effect.³ Glucosamine is widely used as a treatment for OA, despite its controversial and conflicting evidence for effect.^{1,4-11} Meta-analyses and systematic reviews have reported potential mild effect of glucosamine on knee and hip OA.^{4-8,10,11} Glucosamine is also increasingly taken by LBP patients.⁹

Glucosamine is hypothesized to restore cartilage and have anti-inflammatory properties.¹² Degenerative lum-

Context Chronic low back pain (LBP) with degenerative lumbar osteoarthritis (OA) is widespread in the adult population. Although glucosamine is increasingly used by patients with chronic LBP, little is known about its effect in this setting.

Objective To investigate the effect of glucosamine in patients with chronic LBP and degenerative lumbar OA.

Design, Setting, and Participants A double-blind, randomized, placebo-controlled trial conducted at Oslo University Hospital Outpatient Clinic, Oslo, Norway, with 250 patients older than 25 years of age with chronic LBP (>6 months) and degenerative lumbar OA.

Interventions Daily intake of 1500 mg of oral glucosamine (n=125) or placebo (n=125) for 6 months, with assessment of effect after the 6-month intervention period and at 1 year (6 months postintervention).

Main Outcome Measures The primary outcome was pain-related disability measured with the Roland Morris Disability Questionnaire (RMDQ). Secondary outcomes were numerical scores from pain-rating scales of patients at rest and during activity, and the quality-of-life EuroQol-5 Dimensions (EQ-5D) instrument. Data collection occurred during the intervention period at baseline, 6 weeks, 3 and 6 months, and again 6 months following the intervention at 1 year. Group differences were analyzed using linear mixed models analysis.

Results At baseline, mean RMDQ scores were 9.2 (95% confidence interval [CI], 8.4-10.0) for glucosamine and 9.7 (95% CI, 8.9-10.5) for the placebo group ($P=.37$). At 6 months, the mean RMDQ score was the same for the glucosamine and placebo groups (5.0; 95% CI, 4.2-5.8). At 1 year, the mean RMDQ scores were 4.8 (95% CI, 3.9-5.6) for glucosamine and 5.5 (95% CI, 4.7-6.4) for the placebo group. No statistically significant difference in change between groups was found when assessed after the 6-month intervention period and at 1 year: RMDQ ($P=.72$), LBP at rest ($P=.91$), LBP during activity ($P=.97$), and quality-of-life EQ-5D ($P=.20$). Mild adverse events were reported in 40 patients in the glucosamine group and 46 in the placebo group ($P=.48$).

Conclusions Among patients with chronic LBP and degenerative lumbar OA, 6-month treatment with oral glucosamine compared with placebo did not result in reduced pain-related disability after the 6-month intervention and after 1-year follow-up.

Trial Registration clinicaltrials.gov Identifier: NCT00404079

JAMA. 2010;304(1):45-52

www.jama.com

bar OA is associated with cartilage destruction and inflammatory processes,^{13,14} and glucosamine could therefore provide benefit. A few trials of the

Author Affiliations are listed at the end of this article.
Corresponding Author: Philip Wilkens, MChiro, Oslo University Hospital, Department of Orthopaedics, FOU, OS, BD, Bygg 73, Kirkeveien 166, Oslo 0460, Norway (philip.wilkens@medisin.uio.no).

See also p 93 and Patient Page.

effect of glucosamine on LBP have been conducted,¹⁵⁻¹⁷ but with methodological limitations like open-label design, small sample size (<40 patients), short intervention period (<4 weeks), multiple diagnoses, and outcomes measures with questionable psychometric properties, the evidence remains inconclusive.

A more robust evaluation is warranted to establish the effect of glucosamine in LBP patients. We conducted a randomized, double-blind, placebo-controlled trial to investigate the effect of a 6-month intake of glucosamine in reducing pain-related disability in patients with LBP and degenerative lumbar OA.¹⁸

METHODS

Patient Recruitment and Inclusion

The trial was conducted at Oslo University Hospital Outpatient Clinic, Oslo, Norway. Recruitment occurred between December 2006 and July 2008 in Oslo and Bergen, Norway, via referrals by general practitioners, physiotherapists, chiropractors, and self-referrals based on 1 newspaper advertisement. The newspaper is read by approximately 40.0% of the population in the trial area.¹⁹

Patients were included when the eligibility criteria had been confirmed. Inclusion criteria were primary concern of nonspecific chronic LBP (defined as the area below the 12th rib and above the gluteal folds),²⁰ LBP for at least 6 months with summed score of at least 3 out of 24 points on the Roland Morris Disability Questionnaire (RMDQ), older than 25 years of age, and written informed consent. Patients with concomitant leg pain were included as long as the LBP pain rating was higher than the leg pain rating.

Additionally, magnetic resonance imaging (MRI) scans no older than 1 year prior to inclusion consisting of at least 1 axial view (T2 weighted) and 2 sagittal views (T1 and T2 weighted) were required for inclusion. The MRIs, without concealment of name, age, and sex, were first analyzed by radiologists who were not part of the research group. Fur-

ther categorizations of the MRI findings and inclusion to the trial were decided by an orthopedic spinal surgeon and a chiropractor. The chiropractor received additional training in analyzing MRIs and conducted an interreliability test with a radiologist. Disagreements between the 2 diagnosticians were resolved by a second orthopedic surgeon. MRI findings indicating a degenerative process were required for inclusion because glucosamine is a preparation targeting joint degeneration. Patients had to fulfill at least 1 of the following MRI criteria: disk signal intensity changes (gray, dark, or black),²¹ reduced disk height compared with adjacent superior disk,²¹ facet joint changes (grade 1 or grade 2),²² modic changes (type 1, type 2 or type 3),²³ or high-intensity zone (present or not present).²⁴

Exclusion criteria included symptomatic intervertebral disk herniation or spinal stenosis, previous lumbar fracture or surgery, pregnancy or breastfeeding, seafood allergy, ongoing psychiatric or somatic disease potentially influencing a patient's pain, and use of any type of glucosamine 1 year prior to enrollment.

Interventions and Follow-up

The trial participants were randomized to receive a daily dose of 1500 mg of glucosamine sulfate (Glucosamine, Pharma Nord, Vejle, Denmark) or placebo administered as three 500-mg capsules, which could be taken one by one throughout the day or all at once over a period of 6 months. Glucosamine sulfate was supplied as white powder in white capsules in white plastic containers. Placebo was identically supplied and consisted mainly of cellulose. After the 6-month intervention period, the participating patients were free to choose LBP management according to their own preference. Patients were permitted to use rescue medication (pain killers or nonsteroidal anti-inflammatory drugs), their existing analgesics, or their usual LBP therapy (eg, manipulation, physiotherapy, massage). Adjunctive management was reported at the subsequent visit.

Follow-up visits occurred at 6 weeks, 3 and 6 months, and 1 year. The 1-year follow-up assessment was conducted by postal questionnaires.

Adherence was assessed by returned capsule count at 3- and 6-month visits. Testing of successful blinding was conducted by asking the participants to indicate whether they had been assigned to either glucosamine or placebo after the trial intervention period.

Primary Outcome Measure

The primary outcome measure used was the Norwegian version of the RMDQ,²⁵ which is a widely used, back-specific, self-administered measure of pain-related disability. Greater levels of disability give higher numbers on a 24-point scale. RMDQ has content and construct validity and internal consistency. It is also reproducible and sensitive to change over time for LBP patients.^{26,27} A 3-point reduction in the total RMDQ was a priori classified as a response to treatment.

Secondary Outcome Measures

Low back and leg pain intensities during activity and at rest were measured using an 11-point numeric pain rating scale (NRS) with 0 indicating no pain and 10 indicating the worst pain imaginable.²⁸ Patients were asked to rate "most severe low back and/or leg pain" during the preceding week.

Health-related quality of life was measured using EuroQol-5 Dimensions (EQ-5D) index and EuroQol-visual analog scale (EQ-VAS).²⁹ The EQ-5D index measures 5 quality-of-life domains on a -0.59 to 1.0 scale and EQ-VAS measures overall health status on a 20-cm 0 to 100 vertical visual analog scale. The global perceived effect of glucosamine was assessed by the patient on a 7-point Likert scale (1, completely recovered; 2, much recovered; to 7, vastly worsened).³⁰

Baseline Characteristics

Background descriptive data, psychological status (Hopkins Symptom Checklist-25),³¹ and fear avoidance behavior (Fear Avoidance Beliefs Questionnaire)³² were collected at baseline only.

Adverse Events and Safety

Any unfavorable change from the patients' pretreatment state was regarded as an adverse event—regardless of relationship to the study medication. Safety monitoring included assessment of adverse events, blood pressure measurements at every visit, and fasting blood glucose and cholesterol levels before and following intervention. Interim analysis and early discontinuation end points were considered unnecessary because previous studies indicated low risks with glucosamine.⁷ Adverse events, withdrawals, and concomitant illnesses were recorded in accordance with good clinical practice guidelines.

Norway regulates glucosamine as a prescription drug only. Therefore, the study complied with the Norwegian Medicines Agency for conducting randomized controlled trials and provided regular reports to the agency. Additionally, the Regional Ethical Committees for Medicine and Health and the Norwegian Data Inspectorate approved the study, which followed the Declaration of Helsinki.

Randomization

An unstratified computer-generated randomization list in blocks of 10 with a 1:1 ratio allocated patients to glucosamine or placebo. Concealment for blinding was achieved by securing and hiding the researchers' code list, which was accessible to the researchers only after the total data collection was complete. The study medication for each randomization number was packaged and labeled by the manufacturer (Pharma Nord), stored by the pharmacy department in the hospital, and dispensed by a research nurse to the patients. When accepted for the trial, each patient selected an envelope with the allocation number inside from several sealed opaque envelopes.

Statistical Analysis

A change in score of 3 points on the RMDQ is considered the lowest level of clinical importance to be used for sample size calculations in trials.²⁷ We estimated that 250 patients should be

enrolled based on a clinically important difference of 3 with 80% power, a 2-sided significance level of .05, and adding 20% for possible dropouts.

Data monitoring was planned before data collection but facilitated afterward. Data analyses, which were performed on an intention-to-treat basis, commenced after data monitoring. Descriptive statistics were used to summarize patients' characteristics at baseline for each group. Means for baseline and follow-up outcomes were calculated

from the raw data. The NRS data for leg pain had skewed distribution (TABLE 1). RMDQ is considered a continuous variable for the linear mixed-effects models that were used to present estimated treatment effect, confidence intervals (CIs), and *P* values for the between-group differences during the intervention period at 6 weeks, 3 and 6 months, and again 6 months after the intervention at 1 year.²⁶ Fixed effects were time and time \times treatment group interaction. Random effects were intercept and

Table 1. Baseline Characteristics^a

Characteristics	No. (%)			<i>P</i> Value
	Glucosamine (n = 125)	Placebo (n = 125)	Total (N = 250)	
Age, mean (SD), y	47.5 (11.5)	49.4 (11.0)	48.5 (11.24)	.19
Female sex	54 (43.2)	67 (53.6)	121 (48.4)	.13
BMI, mean (SD) ^b	25.4 (4.0)	25.4 (4.6)	25.4 (4.3)	.98
Nonsmokers	106 (84.8)	102 (81.6)	208 (83.2)	.61
Attended college	74 (59.2)	69 (55.2)	143 (57.2)	.53
Married	82 (65.6)	80 (64.0)	162 (64.8)	.79
Employment status				
Full- or part-time	91 (72.8)	91 (72.8)	182 (72.8)	.63
Retired	7 (5.6)	10 (8.0)	17 (6.8)	^c
Disability pension	9 (7.2)	7 (5.4)	16 (6.3)	^c
Sick leave	13 (10.4)	14 (11.2)	27 (10.8)	^c
Other	5 (4.0)	5 (4.0)	10 (4.0)	^c
Clinical characteristics				
Duration of LBP, mean (SD), mo ^d	159.8 (125.3)	160.1 (132.0)	159.9 (128.6)	
LBP 6-48 mo	33 (26.4)	32 (25.6)	32.5 (26.0)	.99
LBP \geq 48 mo	92 (73.6)	93 (74.4)	92.5 (74.0)	^c
Modic changes (any type)	85 (68.0)	80 (64.0)	165 (66.0)	.50
Presence of high intensity zone/annulus tear	41 (32.8)	56 (44.9)	97 (38.9)	.07
Disk signal (any change)	119 (95.2)	119 (95.2)	238 (95.2)	>.99
Disk height (any reduction)	92 (73.6)	81 (64.8)	173 (69.2)	.13
Facet changes (any change)	75 (60.0)	79 (62.9)	154 (61.5)	.71
Pain rating scale, range				
RMDQ, 0-24, mean (SD)	9.2 (3.9)	9.7 (4.5)	9.5 (4.2)	.37
NRS LBP at rest, 0-10, mean (SD)	3.7 (2.6)	3.9 (2.4)	3.8 (2.3)	.48
NRS leg pain at rest, 0-10, mean (SD)	1.8 (2.2)	2.0 (2.3)	1.9 (2.2)	.57
Median (IQR)	1 (0-3)	2 (0-4)	NA	NA
NRS LBP when active, 0-10, mean (SD)	4.9 (2.5)	5.1 (2.3)	5.0 (2.4)	.65
NRS leg pain when active, 0-10, mean (SD)	2.4 (2.6)	2.7 (2.6)	2.5 (2.6)	.51
Median (IQR)	1 (0-3)	2 (0-5)	NA	NA
HSCL-25, 1-4, mean (SD)	1.46 (0.40)	1.46 (0.40)	1.46 (0.40)	.93
FABQ physical activity, 0-24, mean (SD)	10.7 (5.1)	9.7 (5.3)	10.2 (5.2)	.13
FABQ work, 0-42, mean (SD)	13.8 (10.3)	11.7 (9.8)	12.8 (10.1)	.11
EQ-5D index, -0.59-1, mean (SD)	0.57 (0.3)	0.63 (0.2)	0.60 (0.3)	.10
EQ-5D VAS, 0-100, mean (SD)	5.8 (2.2)	6.4 (2.0)	6.1 (2.1)	.02

Abbreviations: BMI, body mass index; EQ-5D, EuroQol-5 Dimensions; FABQ, Fear Avoidance Beliefs Questionnaire; HSCL-25, Hopkins Symptom Checklist; IQR, interquartile range; LBP, low back pain; NA, not applicable; NRS, Numerical Rating Scale; RMDQ, Roland Morris Disability Questionnaire; VAS, visual analog scale.

^aValues are presented as No. (%) unless otherwise specified (mean [SD]; or median [IQR]).

^bBMI is calculated as weight in kilograms divided by height in meters squared.

^cNo *P* value given between subgroups of 1 category.

^dMean (SD) values for duration of LBP indicate patients with long-standing LBP. Conversion is 13.3 (10.4) years for glucosamine, 13.3 (11) years for placebo, and 13.3 (10.7) years for the total category.

random slope. RMDQ observations for every follow-up visit were included and the model was adjusted for RMDQ at baseline, since baseline is assumed to affect the outcome. Unstructured components analysis was used to account for within-subject correlation over time because it produced the lowest Akaike number. Assumptions were assessed by residual analysis.

Secondary outcomes were also assessed using linear mixed-effects models. Data across all measurements, with adjustment for the baseline value in question, were included. The secondary outcomes were assessed for normal distribution, which indicated that parametric statistics were appropriate. Missing values were considered missing at random or completely at random.

Nonmixed models analyses (eg, independent *t* tests, Pearson χ^2 tests, odds ratios) were performed with multiple imputation. Analyses were performed with SPSS version 17.0 for Windows (SPSS, Inc, Chicago, Illinois).

RESULTS

Patient Characteristics

A total of 473 patients were screened, and 250 were included and randomized (FIGURE 1). Reasons for exclusion were LBP as a secondary complaint (*n*=153), previous spinal surgery (*n*=38), a total RMDQ score of less than 3 points (*n*=23), refusal of randomization (*n*=5), and no MRI findings (*n*=4). The groups were similar at baseline, except for EQ-5D VAS, in which an independent *t* test revealed significant difference (Table 1).

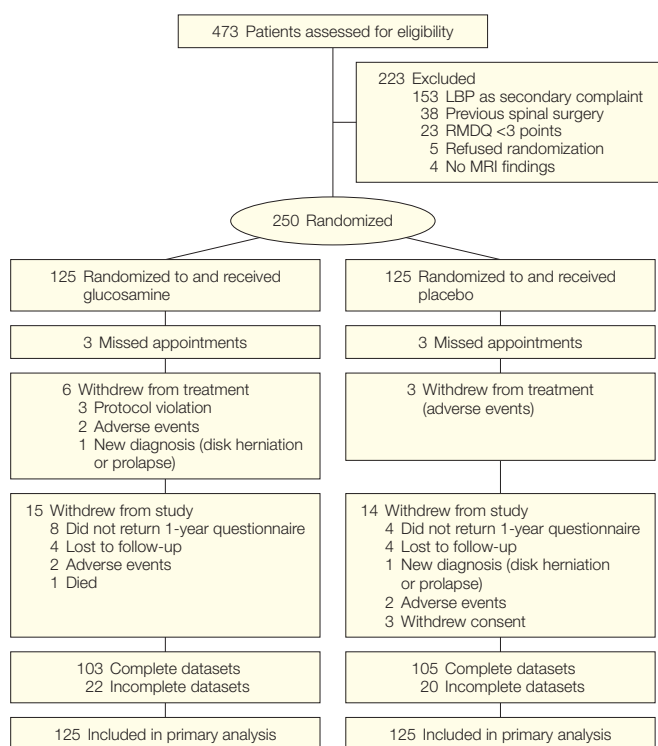
Disability, Pain, and Quality of Life

Baseline RMDQ score for the glucosamine group was 9.2 (95% CI, 8.4-10.0) and 9.7 (95% CI, 8.9-10.5) for placebo. The 6-month RMDQ score was 5.0 (95% CI, 4.2-5.8) for the glucosamine group and 5.0 (95% CI, 4.2-5.8) for placebo. The 1-year RMDQ score was 4.8 (95% CI, 3.9-5.6), for the glucosamine group and 5.5 (95% CI, 4.7-6.4) for placebo. There was no significant time \times treatment interaction for glucosamine vs placebo at the end of the intervention period (6 months) or at 1-year follow-up for RMDQ, NRS LBP, EQ-5D, and EQ-5D VAS (TABLE 2). No difference was found between glucosamine and placebo in terms of minimal important clinical change for the main outcomes (FIGURE 2).

Adherence, Dosage, and Safety

The attrition rate was 6.8% (17 of 250) with 7 and 10 patients in the glucosamine and the placebo group during the intervention period, respectively. At 6 weeks, 4 patients had discontinued the trial in the glucosamine group and 3 in the placebo group (*P*=.70). At 12 weeks, 3 more patients in the placebo group left the trial (*P*=.52). At 6-month follow-up, 3 more patients discontinued the trial in the glucosamine group and 4 more in the placebo group (*P*=.79). There were 15 patients in the glucosamine group and 14 in placebo who did not complete and return the 1-year postal questionnaire. Of all the patients (*n*=208), 44.2% (92) guessed they received glucosamine as the study medication. However, of those receiving glucosamine, 52.4% (54 of 103) correctly guessed their medication and 62.9% of those receiving placebo (66 of 105) correctly guessed their medication allocation (*P*=.06). Medication adherence was similar in the 2 groups with average dose for both groups of 81.5% at 3 months and 87.0% at 6 months. Adverse events (*n*=86) were mild and consisted mostly of gastrointestinal (flatulence, abdominal pain, nausea/vomiting, constipation, and

Figure 1. Enrollment and Outcomes



Patients listed as having withdrawn from treatment discontinued the assigned intervention but continued to undergo trial assessments. Those listed as having withdrawn from the trial discontinued the intervention and assessments. Incomplete data sets reflect the number of missing questionnaires and not the actual number of individuals withdrawing from treatment or study. LBP indicates low back pain; RMDQ, Roland Morris Disability Questionnaire; MRI, magnetic resonance imaging.

diarrhea) and dermatologic problems (TABLE 3). All adverse events were self-limiting without treatment and resolved either with discontinuation (n=10) or continuation of the study drug (n=7). In terms of serious adverse events, 1 patient in the glucosamine group died and 1 participant in each group developed a disk herniation (new diagnosis) and underwent surgery. These events were not considered to be study related. Fasting blood glucose and cholesterol and blood pressure levels did not deviate from normal fluctuations during the trial.

Concomitant Medication and Treatment

Among participants in the glucosamine group during the intervention period, 38.4% (48 of 125) used analgesics, 53.6% (67 of 125) used concomitant therapy, and 28.0% (35 of 125) used both analgesics and concomitant therapy. Corresponding results in the placebo group were 45.6% (57 of 125), 53.6% (67 of 125), and 28.0% (35 of 125) (Table 3).

Among patients in the glucosamine group after the intervention period, 16.0% (20 of 125) used some type of glucosamine preparation, 29.6% (37 of 125) used analgesics, 64.0% (80 of 125) used concomitant therapy, and 50.4% (63 of 125) used a combination of glucosamine, analgesics, or therapy. Corresponding reports in the placebo group were 20.8% (26 of 125), 32.0% (40 of 125), 55.2% (69 of 125), and 58.4% (73 of 125) (Table 3). Both users and nonusers of concomitant management (medication and therapy) improved with 4.5 points on the RMDQ after the 6-month intervention period and 4.3 points at 1-year follow-up.

COMMENT

To our knowledge, this is the first large, long-term trial investigating the efficacy of glucosamine in patients with chronic LBP. Our findings suggest that glucosamine is not associated with a significant difference in pain-related disability, low back and leg pain, health-

Table 2. Primary and Secondary Outcomes

Assessment (Range) and Time of Evaluation	Mean SD (95% CI) ^a			P Value ^c
	Glucosamine (n = 125)	Placebo (n = 125)	Treatment Effect ^b	
RMDQ (0 to 24)				
Baseline	9.2 (8.4 to 10.0)	9.7 (8.9 to 10.5)	NA	NA
6 wk	7.0 (6.1 to 7.8)	7.1 (6.3 to 7.9)	-0.1 (-1.3 to 1.0)	.82
3 mo	5.8 (5.0 to 6.6)	6.5 (5.7 to 7.3)	-0.7 (-1.8 to 0.5)	.24
6 mo	5.0 (4.2 to 5.8)	5.0 (4.2 to 5.8)	0.0 (-1.1 to 1.2)	.72
1 y	4.8 (3.9 to 5.6)	5.5 (4.7 to 6.4)	-0.8 (-2.0 to 0.4)	.50
NRS LBP at rest (0 to 10)				
Baseline	3.7 (3.3 to 4.1)	3.9 (3.5 to 4.3)	NA	NA
6 wk	2.9 (2.5 to 3.3)	2.9 (2.5 to 3.3)	-0.0 (-0.6 to 0.5)	.93
3 mo	2.7 (2.4 to 3.1)	2.9 (2.5 to 3.3)	-0.2 (-0.1 to 0.4)	.54
6 mo	2.5 (2.1 to 2.9)	2.4 (2.0 to 2.8)	0.1 (-0.5 to 0.6)	.91
1 y	2.5 (2.1 to 2.9)	2.8 (2.4 to 3.1)	-0.3 (-0.8 to 0.3)	.85
NRS leg pain at rest (0 to 10)				
Baseline	1.8 (1.5 to 2.2)	2.0 (1.6 to 2.3)	NA	NA
6 wk	1.3 (1.0 to 1.7)	1.5 (1.2 to 1.9)	-0.2 (-0.7 to 0.3)	.42
3 mo	1.4 (1.0 to 1.8)	1.7 (1.4 to 2.1)	-0.3 (-0.9 to 0.2)	.20
6 mo	1.4 (1.0 to 1.7)	1.5 (1.1 to 1.8)	-0.1 (-0.6 to 0.4)	.59
1 y	1.5 (1.1 to 1.8)	1.6 (1.3 to 2.0)	-0.2 (-0.7 to 0.4)	.93
NRS LBP when active (0 to 10)				
Baseline	4.9 (4.5 to 5.3)	5.1 (4.7 to 5.5)	NA	NA
6 wk	3.7 (3.2 to 4.1)	3.6 (3.2 to 4.0)	0.1 (-0.5 to 0.6)	.85
3 mo	3.3 (2.9 to 3.7)	3.2 (2.8 to 3.6)	0.1 (-0.5 to 0.6)	.85
6 mo	3.1 (2.7 to 3.5)	2.9 (2.5 to 3.3)	0.2 (-0.4 to 0.8)	.97
1 y	3.0 (2.5 to 3.4)	2.9 (2.5 to 3.3)	0.1 (-0.5 to 0.6)	.90
NRS leg pain when active (0 to 10)				
Baseline	2.4 (2.0 to 2.8)	2.7 (2.3 to 3.0)	NA	NA
6 wk	1.8 (1.4 to 2.2)	1.9 (1.5 to 2.3)	-0.2 (-0.8 to 0.4)	.53
3 mo	1.7 (1.2 to 2.1)	1.9 (1.5 to 2.3)	-0.2 (-0.8 to 0.4)	.53
6 mo	1.6 (1.2 to 2.0)	1.9 (1.5 to 2.3)	-0.3 (-0.9 to 0.3)	.61
1 y	1.7 (1.3 to 2.1)	2.0 (1.5 to 2.4)	-0.3 (-0.8 to 0.3)	.95
EQ-5D index (-0.59 to 1.0)				
Baseline	0.63 (0.57 to 0.66)	0.57 (0.53 to 0.61)	NA	NA
6 wk	0.68 (0.64 to 0.72)	0.69 (0.65 to 0.72)	0.0 (-0.1 to 0.1)	.83
3 mo	0.73 (0.70 to 0.77)	0.69 (0.65 to 0.73)	0.0 (0.0 to 0.1)	.14
6 mo	0.74 (0.70 to 0.78)	0.76 (0.72 to 0.80)	0.0 (-0.1 to 0.0)	.20
1 y	0.74 (0.70 to 0.78)	0.70 (0.65 to 0.74)	0.0 (0.0 to 0.1)	.07
EQ-5D VAS (0 to 100)				
Baseline	6.4 (5.9 to 7.0)	5.8 (5.3 to 6.4)	NA	NA
6 wk	6.8 (6.2 to 7.3)	6.7 (6.1 to 7.2)	0.1 (-0.7 to 0.9)	.84
3 mo	7.2 (6.7 to 7.8)	6.8 (6.2 to 7.3)	0.4 (-0.3 to 1.3)	.26
6 mo	7.2 (6.6 to 7.8)	7.1 (6.7 to 7.4)	-0.1 (-1.3 to 0.3)	.25
1 y	7.4 (7.0 to 7.7)	6.6 (6.3 to 7.0)	0.7 (0.2 to 1.2)	.14
Global perceived effect, No. (%) ^d				
Baseline	NA	NA	NA	NA
6 wk	22 (18.6)	27 (22.0)	NA	.52
3 mo	26 (21.5)	26 (22.2)	NA	.89
6 mo	39 (33.1)	42 (36.2)	NA	.61
1 y	34 (30.9)	32 (29.4)	NA	.30

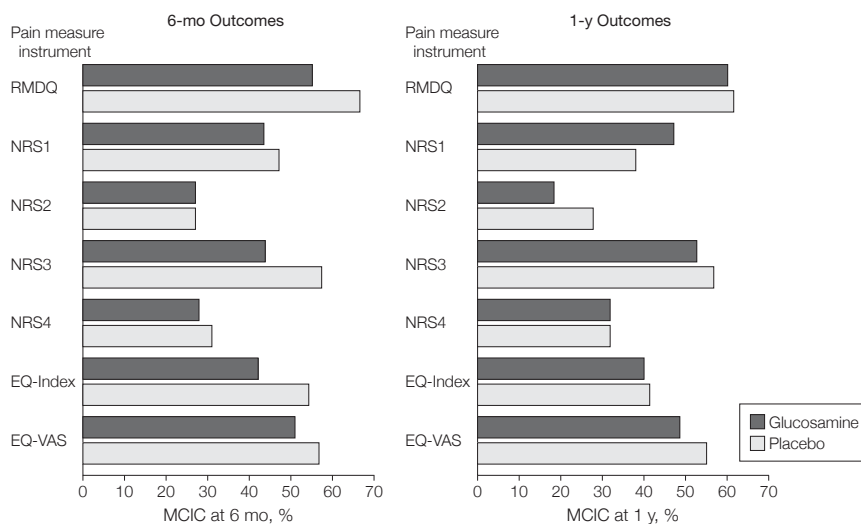
Abbreviations: CI, confidence interval; EQ-5D, Euroqol-5 Dimensions; GPART, global perceived effect of treatment; LBP, low back pain; NA, not applicable; NRS, Numerical Rating Scale; RMDQ, Roland Morris Disability Questionnaire; VAS, visual analog scale.

^aMean SD based on raw data unless stated otherwise; 95% CI estimated/calculated from linear mixed models for continuous variables and Pearson χ^2 for categorical outcomes.

^bTreatment effect for RMDQ, NRS LBP at rest and when active, NRS leg pain at rest and when active, favors glucosamine when values are negative and favors placebo when values are positive. Treatment effect for EQ-5D Index and EQ-5D VAS favors glucosamine when values are positive and placebo when values are negative.

^cP values were estimated/calculated from linear mixed models for continuous variables and Pearson χ^2 for categorical outcomes.

^dValues are the proportion of patients who had a global perceived effect to the intervention, which was defined as a score of 1 (completely improved) or 2 (much improved) on the Global Perceived Effect of Treatment (range, 1 to 7) with lower scores indicating more improvement compared with baseline.

Figure 2. Percentage of Participants With Minimal Clinically Important Change for Main Primary and Secondary Outcomes at 6 Months and 1 Year

Scale ranges and minimal clinical important change (MCIC [the smallest difference in score that patients perceive as beneficial]): Roland Morris Disability Questionnaire²⁵ (RMDQ [range, 0-24; MCIC, 3]); Numerical Rating Scale²⁶ (NRS [range, 0-10; MCIC, 2]); EuroQol-5 Dimensions Index²⁷ (EQ-5D [range, -0.59 to 1.0; MCIC, 0.9]); and EuroQol visual analog scale²⁷ (EQ-VAS [range, 1-100; MCIC, 10.0]). NRS1 indicates low back pain at rest; NRS2, leg pain at rest; NRS3, low back pain when active; and NRS4, leg pain when active.

related quality of life, global perceived effect of treatment, or use of concomitant medications or therapy.

Approximately 30.0% of the patients reported mild adverse events. Only 10 of these patients withdrew from treatment or study during the intervention period, all due to well-known adverse events. Withdrawals and reported adverse events were similar in both groups. A MEDLINE search via PubMed in December 2009 indicated that 3 previous studies have evaluated the efficacy of glucosamine for chronic LBP.¹⁵⁻¹⁷ Our results did not replicate the findings of 2 of the trials, and the authors of the third study¹⁶ made no conclusion due to the small sample size. There may be several explanations for the lack of efficacy of glucosamine in the present trial.

The inclusion criteria for the present trial may have selected patients with LBP who were not receptive to glucosamine, but we believe one of the strengths of this study is a large sample size with patients broadly representative of patients with chronic LBP with lumbar OA and degenera-

tion. The etiology of LBP is incompletely understood,³ therefore LBP studies are faced with a diagnostic challenge and several possible classification methods. Alternative inclusion criteria might have provided a more glucosamine-receptive population. The 2 previous trials reporting an effect with glucosamine did not select patients on the basis of pain-related disability, while the present study and the study with no conclusion of effect did select on this basis.¹⁵⁻¹⁷ However, the potential discrepancy in the patients' disability alone may not fully explain the difference in results because the 3 previous studies were pilot studies in design and methodology. Regardless of a possible alternative LBP population, the participants included in this trial are likely to be a representative sample of the LBP population presenting in general clinical practice.

Glucosamine may be more effective in other body articulations than in the lumbar spine. Several studies indicate effect of glucosamine sulfate in treatment for knee OA.³³ The results from the Glucosamine/chondroitin Arthri-

tis Intervention Trial (GAIT) also implies that glucosamine might be more effective for moderate to severe knee pain than for minimal to moderate knee pain.¹ In addition, OA of the knee contains more of the proinflammatory target for glucosamine than OA of the hip.³⁴ Because the OA disease process and the potential mechanism of glucosamine action are not yet completely understood,^{2,12} the location and severity of OA disease may be important for the efficacy of glucosamine.

Our findings, other knee, hip, or knee and hip OA studies, and 1 meta-analysis suggest that glucosamine has no effect on OA.^{35,36} However, the only similarity between our study and these other trials is the results; patient groups are not comparable.

In contrast, 5 meta-analyses and several studies, including 2 Cochrane reviews and the Glucosamine Unum in Die Efficacy (GUIDE) study, have indicated that glucosamine has some efficacy for hip and knee OA^{4-8,10,11} despite certain weaknesses.^{5,7} Methodological weaknesses, such as lack of allocation concealment, double-blinding, intention-to-treat principle, adequate power, masking of study agent, different study preparations, and consistency between scales may explain this inconsistency.^{1,7,36} Meta-analyses can also have methodological inadequacies from overestimation of the effects due to publication bias or bias within the published studies.³⁷ Latent sponsorship bias has also been suggested as influencing outcomes,³⁶ but an evidence-based, expert consensus guideline found that the scientific evidence for this notion is limited.³⁸

Other strengths of this study are the double-blind design, high adherence rate, lack of industry involvement, 6-month and 1-year follow-up, intention-to treat analysis, and independent data monitoring. Glucosamine is considered a prescription drug in Norway and issues with potential contamination of over-the-counter products is reduced. Successful randomization was indicated by well-balanced groups at baseline with the exception of 1 vari-

able. Empirical evidence suggests that 5% of baseline data will differ significantly by chance.³⁹ Nonsignificant difference ($P=.06$) between the groups, when testing for success of blinding, and group similarity for attrition and adverse events indicate successful blinding. The 6.8% attrition rate was better than the predicted 20.0%.

Trial limitations require attention. First, free participation, including study treatment and visits, and the focus on glucosamine may attract a certain type of patients with specific personality traits toward trial settings and glucosamine that could affect the outcome. Second, adjunctive management was permitted, which may have influenced outcome. Third, adherence was assessed by capsule counts. This may have caused bias owing to increased study awareness and the number of capsules might have been altered by capsule dumping. Fourth, although the capsule counts indicated that more than 80% of the capsules were consumed, the dose-response for glucosamine might require higher adherence to demonstrate efficacy.⁴⁰ The number of returned capsules may also not accurately indicate consumption, but was the preferred option in this trial because of its feasibility, cost, and convenience. Finally, our study was not intended to clarify the pharmacokinetics for glucosamine, but merely to indicate a potentially effective path for clinical practice.

CONCLUSION

No significant differences were found between glucosamine and placebo during the intervention period or at 1-year follow-up. Both interventions improved functional status by the end of treatment by a similar amount. No serious adverse events were associated with either of the study agents. Based on our results, it seems unwise to recommend glucosamine to all patients with chronic LBP and degenerative lumbar OA. Further research is needed to clarify whether glucosamine is advantageous in an alternative LBP population.

Table 3. Distribution of Concomitant Management and Adverse Events During the Trial Period

Variables	No. (%)		OR (95% CI)	P Value
	Glucosamine	Placebo		
Medication Use				
None				
6 wk	85 (68.0)	89 (71.2)	1.14 (0.65-2.00)	.64
3 mo	97 (77.6)	85 (68.0)	0.62 (0.34-1.13)	.31
6 mo	91 (72.8)	82 (65.6)	0.68 (0.38-1.21)	.39
1 y	88 (70.4)	85 (68.0)	0.81 (0.41-1.56)	.50
Over-the-counter preparation				
6 wk	12 (9.6)	16 (12.8)	0.72 (0.33-1.60)	.47
3 mo	10 (8.0)	12 (9.6)	0.80 (0.33-1.94)	.51
6 mo	10 (8.0)	15 (12.0)	0.64 (0.27-1.48)	.44
1 y	12 (9.6)	10 (8.0)	1.22 (0.51-2.94)	.66
Prescription				
6 wk	28 (22.4)	27 (21.0)	1.10 (0.60-2.00)	.76
3 mo	18 (14.4)	22 (17.6)	0.74 (0.38-1.45)	.38
6 mo	19 (15.2)	27 (21.6)	0.65 (0.34-1.24)	.19
1 y	19 (15.2)	19 (15.2)	1.00 (0.50-2.00)	.52
Any type of glucosamine 6 mo-1 y ^a	20 (16.0)	26 (20.8)	0.73 (0.38-1.40)	.40
Concomitant Therapy				
No therapy				
6 wk	69 (55.2)	70 (56.0)	1.01 (0.61-1.69)	.96
3 mo	78 (62.4)	75 (60.0)	0.94 (0.56-1.59)	.82
6 mo	71 (56.8)	76 (60.8)	1.20 (0.71-2.03)	.50
1 y	65 (52.0)	56 (44.8)	0.71 (0.41-1.20)	.20
Chiropractic				
6 wk	25 (20.0)	33 (26.4)	0.70 (0.39-1.27)	.38
3 mo	22 (17.6)	25 (20.0)	0.84 (0.44-1.58)	.50
6 mo	28 (22.4)	25 (20.0)	0.84 (0.44-1.58)	.51
1 y	24 (19.2)	33 (26.4)	0.66 (0.36-1.21)	.42
Physiotherapy				
6 wk	23 (18.4)	13 (10.4)	1.97 (0.95-4.10)	.07
3 mo	20 (16.0)	16 (12.8)	1.28 (0.63-2.60)	.50
6 mo	20 (16.0)	16 (12.8)	1.28 (0.62-2.60)	.50
1 y	15 (12.0)	20 (16.0)	0.71 (0.35,1.47)	.50
Massage				
6 wk	18 (14.4)	27 (21.6)	0.62 (0.32-1.19)	.31
3 mo	20 (16.0)	16 (12.8)	1.28 (0.63-2.60)	.50
6 mo	20 (16.0)	16 (12.8)	1.28 (0.63-2.60)	.50
1 y	10 (8.0)	16 (12.8)	0.60 (0.26-1.39)	.44
Adverse events ^b				
Resulting in study agent termination	4 (3.2)	6 (4.8)	0.66 (0.48-1.36)	.52
Any type	40 (32.0)	46 (36.8)	0.83 (0.49-1.40)	.48
Skin problems	12 (32.0)	15 (12.0)	0.79 (0.35-1.76)	.56
Neurological effects	13 (10.4)	19 (15.2)	0.65 (0.31-1.38)	.26
Heartburn	1 (0.8)	1 (0.8)	0.99 (0.06-15.9)	.99
Flatulence	7 (5.6)	12 (9.6)	0.55 (0.21-1.44)	.22
Abdominal pain	4 (3.2)	3 (2.4)	1.32 (0.29-6.04)	.72
Nausea/vomiting	7 (5.6)	4 (3.2)	1.77 (0.50-6.21)	.37
Constipation	4 (3.2)	1 (0.8)	4.03 (0.44-36.69)	.18
Diarrhea	4 (3.2)	7 (5.6)	0.55 (0.16-1.92)	.34
Headache/vertigo	5 (4.0)	5 (4.0)	0.98 (0.28-3.49)	.98
Musculoskeletal concerns	5 (4.0)	11 (8.8)	0.42 (0.14-1.25)	.11

Abbreviations: CI, confidence interval; OR, odds ratio.

^aRefers to intake of any type of glucosamine postintervention.

^bEvents may not sum because some patients experienced more than 1.

Author Affiliations: Department of Orthopaedics, Oslo University Hospital, and University of Oslo, Oslo, Norway (Mr Wilkens and Drs Grundnes, Hellum, and Storheim); SINTEF Health Research, Oslo, Norway (Dr Scheel); Norwegian Research Center for Active Rehabilitation (NAR), Oslo, Norway (Mr Wilkens and Dr Storheim). Dr Grundnes is now with Hjelp 24 NIMI, Oslo, Norway.

Author Contributions: Mr Wilkens had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wilkens, Scheel, Grundnes, Hellum, Storheim.

Acquisition of data: Wilkens, Storheim.

Analysis and interpretation of data: Wilkens, Scheel, Grundnes, Hellum, Storheim.

Drafting of the manuscript: Wilkens, Scheel, Hellum, Storheim.

Critical revision of the manuscript for important intellectual content: Wilkens, Scheel, Grundnes, Hellum, Storheim.

Statistical analysis: Wilkens.

Obtained funding: Wilkens, Scheel, Grundnes, Storheim.

Administrative, technical, or material support: Wilkens, Storheim.

Study supervision: Wilkens, Scheel, Grundnes, Hellum, Storheim.

Financial Disclosures: None reported.

Funding/Support: The study was supported by grants from the EXTRA funds from the Norwegian Foundation for Health and Rehabilitation through the Norwegian Low Back Pain Association, Norwegian Chiropractic Associations Research Fund, and Wilhelmsens Research Fund. The study medications (glucosamine and placebo) were produced by and purchased from Pharma Nord. Pharma Nord was chosen as the study agent supplier after all companies with marketing approvals in Norway were asked if they wanted to contribute with their product to the trial.

Role of the Sponsor: The Norwegian Foundation for Health and Rehabilitation, the Norwegian Low Back Pain Association, Norwegian Chiropractic Associations Research Fund, and Wilhelmsens Research Fund had no role in design or conduct of the study, collection or analysis of the data, or preparation of the manuscript. Pharma Nord had no involvement in conducting the study, or publishing results from the study.

Additional Contributions: We thank the patients who participated in the trial, the support from Oslo University Hospital Ullevål, and the referring health personnel. We would also like to thank Leiv Sandvik, PhD (professor in biostatistics, Oslo University Hospital), for statistical advice, and Irene Syse, BSN (Oslo University Hospital), for data monitoring, for which they received no compensation. Additionally, we would like to thank Lucy Hyatt, PhD, for critically editing the manuscript, for which she received £275.

REFERENCES

- Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med*. 2006;354(8):795-808.
- Borenstein D. Does osteoarthritis of the lumbar spine cause chronic low back pain? *Curr Pain Headache Rep*. 2004;8(6):512-517.
- Deyo RA, Weinstein JN. Low back pain. *N Engl J Med*. 2001;344(5):363-370.
- Lee YH, Woo JH, Choi SJ, Ji JD, Song GG. Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis. *Rheumatol Int*. 2009;30(3):357-363.
- McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. *JAMA*. 2000;283(11):1469-1475.
- Richy F, Bruyere O, Ethgen O, Cucherat M, Henrotin Y, Reginster JY. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. *Arch Intern Med*. 2003;163(13):1514-1522.
- Towheed TE, Maxwell L, Anastassiades TP, et al. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev*. 2005;(2):CD002946.
- Towheed TE, Anastassiades TP, Shea B, et al. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev*. 2001;(1):CD002946.
- Hopman WM, Towheed TE, Gao Y, et al. Prevalence of and factors associated with glucosamine use in Canada. *Osteoarthritis Cartilage*. 2006;14(12):1288-1293.
- Herrero-Beaumont G, Román JA, Trabado MC, et al. Effects of glucosamine sulfate on 6-month control of knee osteoarthritis symptoms vs placebo and acetaminophen: results from the Glucosamine Unum In Die Efficacy (GUIDE) trial [abstract]. *Arthritis Rheum*. 2005;9(suppl):1203. doi:10.1016/S1063-4584(05)80353-X.
- Herrero-Beaumont G, Ivorra JA, Del Carmen Trabado M, et al. Glucosamine sulfate in the treatment of knee osteoarthritis symptoms: a randomized, double-blind, placebo-controlled study using acetaminophen as a side comparator. *Arthritis Rheum*. 2007;56(2):555-567.
- Largo R, Alvarez-Soria MA, Diez-Ortego I, et al. Glucosamine inhibits IL-1beta-induced NFkappaB activation in human osteoarthritic chondrocytes. *Osteoarthritis Cartilage*. 2003;11(4):290-298.
- Igarashi A, Kikuchi S, Konno S. Correlation between inflammatory cytokines released from the lumbar facet joint tissue and symptoms in degenerative lumbar spinal disorders. *J Orthop Sci*. 2007;12(2):154-160.
- Le Maitre CL, Pockert A, Buttle DJ, Freemont AJ, Hoyland JA. Matrix synthesis and degradation in human intervertebral disc degeneration. *Biochem Soc Trans*. 2007;35(Pt 4):652-655.
- Drovanti A, Bignamini AA, Rovati AL. Therapeutic activity of oral glucosamine sulfate in osteoarthritis: a placebo-controlled double-blind investigation. *Clin Ther*. 1980;3(4):260-272.
- Leffler CT, Philippi AF, Leffler SG, Mosure JC, Kim PD. Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: a randomized, double-blind, placebo-controlled pilot study. *Mil Med*. 1999;164(2):85-91.
- Tant L, Gillard B, Appelboom T. Open-label, randomized, controlled pilot study of the effects of a glucosamine complex on low back pain. *Current Therapeutic Res*. 2005;66(6):511-521. doi:10.1016/j.curtheres.2005.12.009.
- Grundnes O; Ullevål University Hospital. The glucosamine-study: the effect of glucosamine in treatment of chronic low back pain (clinicaltrials.gov identifier, NCT 00404079). <http://clinicaltrials.gov/ct2/results?term=NCT+00404079>. Accessed May 11, 2009.
- European Journalism Centre. Media landscape—Norway. http://www.ejc.net/media_landscape/article/norway/. Accessed June 10, 2010.
- van Tulder M, Becker A, Bekkering T, et al. Chapter 3: European guidelines for the management of acute nonspecific low back pain in primary care. *Eur Spine J*. 2006;15(suppl 2):s169-s191.
- Luoma K, Riihimäki H, Luukkainen R, Raininko R, Viikari-Juntura E, Lamminen A. Low back pain in relation to lumbar disc degeneration. *Spine*. 2000;25(4):487-492.
- Pathria M, Sartoris DJ, Resnick D. Osteoarthritis of the facet joints: accuracy of oblique radiographic assessment. *Radiology*. 1987;164(1):227-230.
- Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. *Radiology*. 1988;166(1 pt 1):193-199.
- Aprill C, Bogduk N. High-intensity zone: a diagnostic sign of painful lumbar marrow on magnetic resonance imaging. *Br J Radiol*. 1992;65(773):361-369.
- Grotle M, Brox JJ, Vollestad NK. Cross-cultural adaptation of the Norwegian versions of the Roland-Morris Disability Questionnaire and the Oswestry Disability Index. *J Rehabil Med*. 2003;35(5):241-247.
- Roland M, Morris R. A study of the natural history of back pain: part I: development of a reliable and sensitive measure of disability in low-back pain. *Spine*. 1983;8(2):141-144.
- Stratford PW, Binkley J, Solomon P, Finch E, Gill C, Moreland J. Defining the minimum level of detectable change for the Roland-Morris questionnaire. *Phys Ther*. 1996;76(4):359-365.
- Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94(2):149-158.
- Solberg TK, Olsen JA, Ingebrigtsen T, Hofoss D, Nygaard OP. Health-related quality of life assessment by the EuroQol-5D can provide cost-utility data in the field of low-back surgery. *Eur Spine J*. 2005;14(10):1000-1007.
- Ostelo RW, de Vet HC. Clinically important outcomes in low back pain. *Best Pract Res Clin Rheumatol*. 2005;19(4):593-607.
- Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav Sci*. 1974;19(1):1-15.
- Waddell G, Newton M, Henderson I, Somerville D, Main CJA. Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. *Pain*. 1993;52(2):157-168.
- Pavelká K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch Intern Med*. 2002;162(18):2113-2123.
- Meulenbelt I, Kloppenburg M, Kroon HM, et al. Clusters of biochemical markers are associated with radiographic subtypes of osteoarthritis (OA) in subject with familial OA at multiple sites the GARP study. *Osteoarthritis Cartilage*. 2007;15(4):379-385.
- Rozendaal RM, Koes BW, van Osch GJ, et al. Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. *Ann Intern Med*. 2008;148(4):268-277.
- Vlad SC, LaValley MP, McAlindon TE, Felson DT. Glucosamine for pain in osteoarthritis: why do trial results differ? *Arthritis Rheum*. 2007;56(7):2267-2277.
- Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. *J Clin Epidemiol*. 2000;53(2):207-216.
- Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage*. 2008;16(2):137-162.
- Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet*. 2000;355(9209):1064-1069.
- Persiani S, Roda E, Rovati LC, Locatelli M, Giacovelli G, Roda A. Glucosamine oral bioavailability and plasma pharmacokinetics after increasing doses of crystalline glucosamine sulfate in man. *Osteoarthritis Cartilage*. 2005;13(12):1041-1049.