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Glucosamine/chondroitin combined with exercise for the treatment of knee osteoarthritis: a preliminary study

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Summary

Objective: This preliminary study sought to determine whether using 1500/1200 mg of glucosamine hydrochloride and chondroitin sulfate (GH/CS) is effective, both separately and combined with exercise, compared to a placebo plus exercise program in improving physical function, pain, strength, balance, and mobility in older adults with knee osteoarthritis (OA).

Methods: This double-blind, placebo-controlled, randomized clinical trial lasted 12 months. Participants included 89 older adults (age $\geq$ 50 years) with knee OA randomized to either GH/CS or placebo group. Phase I was a 6-month trial comparing the effects of assignment to either GH/CS or placebo. Phase II added 6 months of exercise for both groups. The primary outcome measure was Western Ontario and McMaster University Osteoarthritis Index (WOMAC) function, and secondary outcome measures included WOMAC pain, 6-min walk, balance, and knee strength.

Results: Of the 89 randomized participants, 72 (81%) completed the study. The median pill compliance was 94% and 95% in Phase I, and, in Phase II, 97% and 91% for the GH/CS and placebo groups, respectively. Median exercise compliance during Phase II was 77% for the GH/CS group and 78% for the placebo group. WOMAC function and pain did not differ significantly between the groups at 6- or 12-month follow-up. There were also no significant differences between the groups in 6-min walk or knee strength; however, balance was better in the placebo group with approximately a 10% difference compared to the GH/CS group.

Conclusions: The GH/CS group was not superior to the placebo group in function, pain, or mobility after both phases of the intervention (pill only and pill plus exercise).

Key words: Glucosamine, Chondroitin, Exercise, Knee osteoarthritis, Nutraceutical, Dietary supplement.

Introduction

Recently, osteoarthritis (OA) treatment using glucosamine and chondroitin has gained widespread use. Classified as prescription drugs in continental Europe, glucosamine and chondroitin are less regulated dietary supplements in the United States and Great Britain. Several studies have shown that glucosamine sulfate was effective in reducing pain and other OA symptoms compared to a placebo[1–3]. In contrast, Rindone *et al.*[4] found no difference in knee pain between glucosamine sulfate and a placebo. The results of several meta-analyses suggest that the effect of glucosamine sulfate ranges from a modest, short-term effect on pain to structural efficacy[5–8]. McAlindon *et al.*[6] noted that the available studies had design and data analysis flaws, including small number of participants, small treatment effects, short duration, publication bias, selective publication of positive trials, unaccounted-for use of concomitant pain medications, and lack of intent-to-treat analysis.

In a more recent meta-analysis, Richy *et al.*[5] concluded that 1500 mg of glucosamine sulfate taken for 3 years slows the degenerative process. This conclusion was based primarily on the strength of two long-term randomized clinical trials that showed significant improvements in self-reported physical function and significantly less OA knee disease progression after 3 years of treatment[2,9]. Preliminary data from the glucosamine unum in die efficacy (GUIDE) trial performed in Europe found patients using glucosamine sulfate for 6 months had significantly less knee pain than a placebo[3]. Recent evidence from the glucosamine/chondroitin arthritis intervention trial (GAIT), a Phase III clinical trial, found no difference in overall Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain scores after 24 weeks of receiving either glucosamine hydrochloride (GH), chondroitin sulfate (CS), glucosamine plus

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chondroitin, celecoxib, or a placebo[10]. A recent Cochrane review concluded that clinical trials using the Rotta Pharmaceutical preparation of glucosamine sulfate were more effective than studies using other glucosamine sulfate formulas; however, the results were not uniformly positive[7].

Some people have suggested that a combination of glucosamine and CS is efficacious in OA. Two studies reported that a combination of glucosamine, chondroitin, and manganese ascorbate significantly improved pain in adults with knee OA[11,12]. Similarly, a combination therapy that included glucosamine, chondroitin, and vitamin C improved temporomandibular joint pain in 40 out of 50 participants[13]. Secondary results from the GAIT trial found a beneficial effect in the combination of glucosamine and chondroitin, however, only in participants with moderate to severe pain[10]. Taken together, these data suggest that glucosamine and chondroitin have beneficial effects (effect sizes 0.44 and 0.78 for glucosamine and chondroitin, respectively) on joint pain from OA[14].

Exercise is a proven non-pharmacologic treatment for knee OA[15]. It results in clinically significant improvements in function, pain, and strength and does not exacerbate disease progression[15–19]. We hypothesized that the effects of glucosamine hydrochloride and chondroitin sulfate (GH/CS) therapy combined with exercise would be additive, resulting in greater improvements in function, pain, and mobility than exercise alone. We proposed a two-phase, short-term, preliminary study in older adults with knee OA to compare the effects of GH plus CS to a placebo (Phase I) on function, pain, mobility, strength, and balance, and the added effects of exercise therapy (Phase II).

Patients and methods

DESIGN

The glucosamine/chondroitin and training exercise study (GATES) was a 12-month, double-blind, placebo-controlled, randomized clinical trial (RCT) of older adults with knee OA. Phase I was a 6-month trial designed to compare the effects of assignment to either a combination of GH/CS or a placebo. Phase II added identical 6-month exercise programs for both groups. The study was conducted at the Wake Forest University Clinical Research Center with the approval of the University's Institutional Review Board.

PARTICIPANT RECRUITMENT

Recruitment techniques included phone calls and mailings to participants in previous knee OA clinical trials who had provided consent for notification of future trials; advertisements in local newspapers; and informational sessions at senior centers, assisted-living facilities, and local churches. Recruitment was open to people aged $\geq$50 years with radiographic evidence of mild to moderate knee OA (Kellgren–Lawrence grade II–III[20]) who met the American College of Theumatology (ACR) classification criteria[21]. Recruitment specifically targeted minority groups by placing ads in a local minority newspaper and sending letters announcing the trial to minority churches. Dates for recruitment were August 2002–December 2003. Recruitment waves began every 3 months and follow-up at 6 (FU6) and 12 (FU12) months. The study ended in December 2004.

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria included age $\geq$ 50 years with radiographic evidence of mild to moderate knee OA (Kellgren–Lawrence grade II–III[20]) who met the ACR clinical[21], and radiographic classification criteria or confirmation of mild to moderate radiographic evidence of knee OA from a personal physician; and not currently participating in another intervention study. Exclusion criteria included dementia (Mini-Mental State Examination [MMSE] $<$ 24); active cancer other than skin cancer; anemia (participants with an hematocrit (HCT) $<$ 32 (or a hemoglobin below 10) were excluded due to possible inability to adequately exercise or the increased potential for increased risk for serious adverse cardiovascular events); severe renal insufficiency (serum creat $>$ 2); hepatic disease (the effects of hepatic disease on the response to exercise or GH/CS that are metabolized in the liver are not well known); excess alcohol use ($\geq$21 alcoholic drinks per week); knee-joint replacement, inability to walk unassisted at least 128 m in 6 min; completion of more than 20 min of formal exercise per week during the past 3 months; planned absence for longer than 2 weeks during required study visits; residing farther than a 1-h drive from the research facilities; inability to swallow a test pill; allergy to shellfish; exposure to glucosamine and/or chondroitin in the 6 months prior to randomization; unwilling to discontinue current arthritis medications during the 2-week washout period and 12-month intervention period, with the exception of a rescue medication; less than 80% compliance rate during run-in period (see Measurements and procedures); failure to complete graded exercise test (GXT); required human assistance with activities related to knee pain (e.g., walking up and down stairs; getting in or out of a chair, etc.); recent knee surgeries, or knee injections such as cortisone and hyaluronic acid; and inability to read or speak English.

Interventions

PHASE I: GH/CS VS PLACEBO

Run-in/washout period

Prior to randomization, participants underwent a 2-week run-in, washout period; that is, they discontinued all over-the-counter or prescription medications. These medications and the number of patients using them at baseline were non-steroidal anti-inflammatory drugs (NSAIDs): 16, 18; acetaminophen: 46, 37; aspirin: 25, 26; narcotic: 4, 1; and migraine analgesic: 5, 3 for the treatment and placebo groups, respectively. Rescue medication (acetaminophen: maximum dosage 4 g d^{-1}) and any other necessary medications unrelated to OA were permitted. All participants received an unblinded 2-week supply of the placebo (three pills per day). At the end of the 2-week period, the bottles were returned to the study staff. Pill compliance was calculated as the number of pills taken/number prescribed. A compliance rate below 80% was an exclusion criterion.

Phase I

After the run-in/washout period, participants were randomized to either a glucosamine/chondroitin group or a placebo control group. The glucosamine/chondroitin group was treated with 1500/1200 mg of unlabeled GH/CS per day for 6 months. The participants were given a choice of either once or three times per day regimens. The control group took a placebo of identical size, color, and shape at the same frequency. Both groups attended six healthy lifestyle classes on such topics as living with OA, healthy eating, and exercise, designed to keep participants interested and involved in the study until the beginning of Phase II. Each participant also met monthly with a research interventionist to monitor study compound and rescue medication use (pill counts), to review

the participant's medication diary, and to give participants an opportunity to voice questions or concerns that they might not have felt comfortable addressing in group sessions. At the end of Phase I, participants repeated the series of tests conducted at baseline. Each participant began Phase II after the 6-month follow-up testing was completed.

PHASE II: GH/CS PLUS EXERCISE VS PLACEBO PLUS EXERCISE

Phase II was a continuation of Phase I intervention with the addition of 6 months of exercise for both groups. The combined facility and home-based exercise program was modeled after our large-scale OA clinical trials, fitness arthritis in seniors trial (FAST) and arthritis diet and activity promotion trial (ADAPT)[15,22]. Facility-based exercise classes were held 2 d week^{-1}, 1 h d^{-1}. Each participant supplemented the facility-based sessions with one home-based session per week. Sessions began and ended with 5-min warm-up and cool-down periods, respectively. The exercise phase included two 15-min walking sessions separated by 20 min of strength training. Participants were provided with an aerobic exercise prescription that included walking within a heart-rate range of 50–75% of heart-rate reserve. Each strength training session consisted of 10–12 repetitions of the following exercises: (1) leg extension, (2) leg curl, (3) heel raise, and (4) step up. Cuff weights and machines provided resistance. Following two orientation sessions, participants began with the lowest possible resistance. Weight was increased in 2.5–5 lb increments, depending on the participant, after two sets of 12 repetitions had been performed for 2 consecutive days. A 1–1.5 min rest interval separated each exercise. American College of Sports Medicine-certified Exercise Leaders supervised each session, and exercise and attendance logs were used to monitor progress.

The home-based exercise mirrored the facility-based sessions. Each participant met individually with one of the Exercise Leaders to discuss exercising at home, and the healthy lifestyle classes conducted in Phase I included information about community-based exercise programs for seniors. If compliance to the home-based program fell below expected levels, the Exercise Leader assisted the participant in an exercise session and discussed the barriers that the participant was encountering. Monthly individual sessions continued during Phase II to monitor compliance with the study supplement and exercise program.

Supplement and placebo allocation

The study sponsor (Rexall Sundown, Inc.) donated the study compound and matching placebo. All study compound bottles received were numbered with a corresponding sealed list including lot numbers and bottle contents (active or placebo). The study compound was allocated in order at the first healthy lifestyle class. A certificate of analysis, issued and approved by the study sponsor's quality-assurance manager and verified by an independent source (Consumer Lab, Inc.), revealed that each study tablet contained GH (503.778 mg/99% glucosamine) and CS (497.388 mg/80% chondroitin). Inactive ingredients included microcrystalline cellulose 102 National Formulary (NF) (6.833 mg), beet powder (12.310 mg), crosprovidone US Pharmacopeia (USP)/NF (10.258 mg), magnesium stearate Food Chemical Codex (FCC) (5.000 mg), and precipitated silica (1.026 mg).

Rescue medication was available during the entire course of the study. Each participant received enough 500 mg tablets of acetaminophen to allow the maximum daily dose of 4 g d^{-1} for pain relief. During a monthly visit with the study coordinator, participants were asked whether they used any rescue medication in the previous month. Participants who required pain control medication in excess of 4 g d^{-1} discussed an alternative plan with the study coordinator and the study physician.

Measurements and procedures

Each subject participated in a series of tests at baseline and at 6- and 12-month follow-up. Two screening visits (SV1 and SV2) were separated by the 2-week run-in/washout period. All staff and participants were blinded to the supplement assignment.

OUTCOME MEASURES

Physical function

The primary outcome was WOMAC self-reported physical function measure. WOMAC uses 17 questions about the degree of difficulty in performing daily living activities (e.g., descending stairs) to assess participants' physical function[23,24]. The Likert (LK) version of the WOMAC asks participants to indicate on a scale from 0 (none) to 4 (extreme) the degree of difficulty they have experienced in the last 48 h due to knee OA. Individual scores for the 17 items are added to generate a summary score that can range from 0 to 68, with higher scores indicating poorer function. This instrument, which also includes questions about pain that were used as secondary outcomes, has been validated and is recommended by the Osteoarthritis Research Society as the measure of choice when assessing health status in older adults with knee OA[24].

Pain

The WOMAC pain subscale assessed a participant's level of pain. It consists of five items, and total scores can range from 0 to 20, with larger scores indicating greater dysfunction. The ratings for pain are identical to the WOMAC physical function scale, ranging from 0 (none) to 4 (extreme).

Mobility

The distance walked in 6 min was our measure of mobility[25]. Participants walked as far as possible in 6 min on an established course.

MMSE

We used the MMSE to assess participants' mental status and to exclude those participants with a score below 24[26].

Strength

We assessed knee concentric extension and flexion strength of the participant's most affected limb using a Kin-Com 125E isokinetic dynamometer (Chattanooga Corp.) set at an angular velocity of at 30° s^{-1}. Prior to testing, a warm-up period habituated participants to the testing equipment. They were secured with the torso and tested leg strapped to the testing chair, hands across the chest, the axis of the dynamometer aligned with the knee, and the

resistance pad attached to the lower leg proximal to the ankle joint. Gravity effect torque was calculated based on the participant's leg weight at a 45° angle.

The activation force for each muscle group was set at 50% maximal voluntary isometric contraction. Strength was measured through a joint range from 90° to 30° (0° = full extension). The first and last 10° were subsequently deleted to account for the acceleration and deceleration of the dynamometer at the ends of the range of motion and to account for inconsistent effort. Hence, average force was the average value between joint angles of 40° and 80°[27]. There was a rest period of 30–60 s between each trial. Two maximally reproducible trials were averaged, and the maximum number of trials for each test was six.

Balance

Balance data were collected as participants stood on an AMTI™ force platform interfaced with a six-channel amplifier and a microcomputer. The force platform was set to sample data at 60 Hz. A template affixed to the force platform surface provided consistent foot placement for stance positions. To control for the effects of footwear, subjects were tested without shoes or socks. A shoulder harness suspended from the ceiling afforded unrestricted movement yet, in the event of total loss of balance, prevented a fall to the floor.

Dynamic balance was defined as the excursion of the center of pressure (COP) in the anteroposterior plane during a forward (Y_{max}) and then backward (Y_{min}) lean. Participants were instructed to lean forward and backward as far as possible, using only the ankle joint[28,29]. The COP excursion is the difference in these maximum values ($COP = Y_{max} - Y_{min}$). These data were normalized by dividing the COP excursion by the subject's foot length. Participants were advised to limit knee and trunk flexion and shoulder abduction. After one practice trial, four trials were recorded, with the results of the last three averaged to yield a representative dynamic balance value.

Demographics

Age, race, education, and income data were acquired by self-report. Information concerning comorbid conditions was based on the participant's medical history, medication use, and physical examination.

Statistical analysis

The trial's primary objective was to determine the effects of glucosamine/chondroitin and glucosamine/chondroitin plus exercise interventions on physical function, pain, and mobility. Primary analyses were conducted by intent-to-treat using the last observation carried forward technique for missing data, with participants analyzed according to their initial assignment. All tests of hypotheses and reported *P*-values were two-sided.

To compare groups, *t* tests were used for continuous demographic or clinical data and Chi-square or Fisher's exact test for categorical data.

The effects of glucosamine/chondroitin at 6 months and glucosamine/chondroitin plus exercise at 12 months post-randomization were determined by repeated measures analysis of covariance (ANCOVA), using SAS statistical package. The main models included follow-up levels as the dependent variables with group, time and their interaction as independent variables, and age, gender, body mass index (BMI) and baseline levels as covariates. Separate models were also fitted for change from baseline adjusting for age, gender, and BMI. *P*-values for group differences at each time period are reported as they reflect the effect of different interventions at the end of each phase (pill only and pill plus exercise). *P*-values for differences over time were obtained from models with no interaction as none were statistically significant. Results from these models are reported in the text only.

Post hoc power calculations were obtained from two-group *t* test of equal means with unequal *n*'s using nQuery Advisor software. We had 80% power to detect an 8.2% difference in 6-min walk distance and a 4.6 (23.1%) unit difference in mean WOMAC function between the two groups at the end of the study.

Median, 25th and 75th percentiles were reported for pill and exercise compliance because of skewed distributions. Compliance was also divided into groups to examine the effects of the interventions within each compliance group. For each outcome, models were fitted using ANCOVA, with age, gender, BMI, and baseline levels as covariates. Fourteen participants were not included because they dropped from the study before Phase II started. For exercise compliance, a 12-month *P*-value was reported as an overall comparison between the high, middle, and low compliant groups.

Change in rescue medication use was reported as a change from baseline in the number of participants taking rescue medication for each group. These data reflect changes in the number of participants reporting the use of rescue medication during the previous intervention period, but do not reflect fluctuations in dosage.

Results

RETENTION AND COMPLIANCE

The total number of persons prescreened *via* telephone or face-to-face interview during the 16-month recruitment period was 865 (Fig. 1). Of these, 89 were randomized, and 776 were either ineligible or declined to participate.

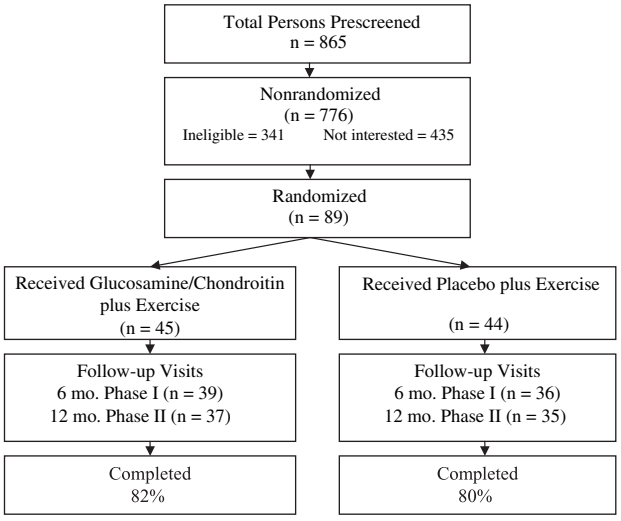

Fig. 1. Progress of participants throughout the trial.

The most common reasons for ineligibility were major health problems that met exclusion criteria (22%), already taking glucosamine or chondroitin (15%), regular exercise of more than 20 min per week (14%), and knee replacement (12%). Of the 89 randomized participants, 72 (81%) completed the study (returned for the final data-collection visit). The most common reasons for withdrawal included lost interest in the study and personal or family health issues. Knee strength was measured on a subset of participants, 29 in the GH/CS group and 25 in the placebo group. The characteristics of the randomized cohort are shown in Table I. The GH/CS participants were significantly younger, more overweight, and had a higher income than the placebo group. Consequently, age and BMI were used as covariates in our statistical analyses. We also included gender as a covariate as outcomes may vary between men and women. The only reported adverse event was hair loss in one participant in the GH/CS group.

CLINICAL OUTCOMES

WOMAC function

Mean function did not vary significantly between groups at 6-month ($P = 0.52$) or 12-month ($P = 0.50$) follow-up (Table II and Fig. 2). However, mean WOMAC function combining both groups improved significantly over time ($P = 0.005$). After 12 months, participants improved 4.6 units (17%) and 2.6 units (12%) on average from baseline in the glucosamine/chondroitin group and the placebo group.

Pain

The placebo group's mean level of pain did not differ significantly from the GH/CS mean level at 6 months ($P = 0.97$) or at 12 months ($P = 0.23$), nor did pain levels significantly change over time for both groups combined ($P = 0.11$).

Mobility

There was no significant difference in 6-min walk distance between the groups at 6 months ($P = 0.80$) or 12 months ($P = 0.91$) (Table II). Both groups made small (5–6%) gains over 12 months. The mean difference over time when averaging both groups was statistically significant ($P = 0.01$).

Medication use

The number of participants who used acetaminophen (our rescue medication) decreased by 28% and 21% in the glucosamine/chondroitin and placebo groups, respectively, at 6-month follow-up, and by 37% and 11% from baseline at 12-month follow-up. There was no change in the use of aspirin, other analgesics, or corticosteroids. Two people in the GH/CS group and three in the placebo group took NSAIDs during the course of the study for pain.

STRENGTH

Mean knee extension strength did not differ significantly between the groups at 6 months ($P = 0.28$) or 12 months ($P = 0.92$) (Table II). The GH/CS group improved mean extension strength during the 6-month exercise program (Phase II), making up for all but 2 N of the loss in strength during Phase I. The placebo group gained 26% overall from baseline after Phase II.

Mean knee flexion strength tended to vary differently over time between the groups. Mean values were not significantly different between the groups at 6 months ($P = 0.95$).

Table I
Demographic and clinical characteristics of study participants, mean ± standard error or frequency (%)

Variables	GH/CS group, $N = 45$	Placebo group, $N = 44$	Range	*P*-value
Age (years)	70.0 ± 1.28	74.1 ± 1.32	52–95	0.03
Baseline BMI ($kg\,m^{-2}$)	30.7 ± 0.93	27.3 ± 0.71	16.9–49.9	0.005
Gender				
Female	34 (75.6)	29 (65.9)		0.31
Male	11 (24.4)	15 (34.1)		
Race				
Caucasian	31 (68.9)	35 (77.3)		0.50
African–American	9 (20.0)	5 (11.4)		
Asian/Pacific Islander	3 (6.7)	1 (2.3)		
Native American	2 (4.4)	3 (6.8)		
Education				
<12 Years	3 (6.8)	3 (7.3)		0.93
12 Years	8 (18.2)	6 (14.6)		
>12 Years	33 (75.0)	32 (78.1)		
Annual household income				
<$15,000	2 (4.94)	6 (17.7)		0.05
$15,000–35,000	11 (24.4)	6 (17.7)		
$35,000–50,000	7 (15.6)	12 (35.3)		
>$50,000	21 (46.7)	10 (29.4)		
Comorbidities				
Cardiovascular disease	16 (35.6)	13 (29.5)		0.55
Hypertension	26 (57.8)	23 (53.3)		0.60
Cancer	8 (17.8)	6 (13.6)		0.59
Diabetes	6 (13.3)	6 (13.6)		0.97
Chronic obstructive pulmonary disease	5 (11.1)	4 (9.1)		0.99

Table II
Between group (GH/CS vs Placebo) effects of the treatment on function, pain, 6-min walk distance, strength, and balance at FU6 and FU12. Means (SE) adjusted for gender, age, baseline value, and BMI

Variable	Group	Baseline*	FU6	*P*-value FU6	FU12	*P*-value FU12
Function	GH/CS	25.9 (1.7)	21.9 (1.1)	0.52	19.4 (1.2)	0.50
	Placebo	21.1 (1.5)	22.9 (1.1)		20.6 (1.2)	
Pain	GH/CS	7.1 (0.5)	6.2 (0.4)	0.97	6.0 (0.5)	0.23
	Placebo	5.9 (0.5)	6.2 (0.4)		5.18 (0.5)	
6-min walk (m)	GH/CS	384.7 (17.6)	393.6 (8.0)	0.80	409.2 (8.7)	0.91
	Placebo	398.7 (17.3)	396.5 (7.9)		410.5 (8.6)	
Knee concentric extension strength (N)	GH/CS	209.4 (31.2)	176.9 (16.3)	0.28	207.6 (14.1)	0.92
	Placebo	163.9 (20.6)	202.7 (17.5)		209.7 (15.0)	
Knee concentric flexion strength (N)	GH/CS	106.0 (16.1)	106.1 (7.3)	0.95	102.9 (7.7)	0.05
	Placebo	83.0 (10.9)	106.7 (7.8)		124.8 (8.3)	
Balance (foot length)	GH/CS	0.52 (0.04)	0.523 (0.014)	0.01	0.538 (0.017)	0.05
	Placebo	0.53 (0.03)	0.583 (0.017)		0.591 (0.020)	

FU6, FU12: follow-up 6 and 12 months. *Theonly significant difference between the two groups at baseline is in function ($P = 0.04$).

During Phase II, knee flexion strength decreased slightly in the GH/CS group (−3 N) and increased 18 N in the placebo group. As a result, the placebo group was significantly ($P = 0.05$) stronger in knee flexion strength at the conclusion of the study (Table II).

BALANCE

There was a significant difference in balance between the groups. The placebo group had significantly better balance than the GH/CS group at 6 months (0.58 vs 0.53, $P = 0.01$) and 12 months (0.59 vs 0.54, $P = 0.05$), respectively.

EFFECTS OF PILL AND EXERCISE COMPLIANCE

The median (25th percentile and 75th percentile) for pill compliance, defined as the number taken divided by the number prescribed, was 94% (84%, 100%) and 95% (79%, 100%) for Phase I, and 97% (80%, 100%) and 91% (71%, 99%) for Phase II for the glucosamine/chondroitin and placebo groups, respectively. Corresponding numbers for exercise compliance during Phase II, defined as the number of sessions completed divided by the number scheduled, were 77% (63%, 90%) for the glucosamine/chondroitin group and 78% (61%, 95%) for the placebo group. Tables IIIA and IIIB show compliance over the entire study. To be considered pill-compliant overall, a participant had to be in the top compliance group (85−100%) during both Phase I (months 0−6) and Phase II (months 7−12) of the study. There were no significant differences between the groups in pill ($P = 0.33$) or exercise ($P = 0.62$) compliance (Tables IIIA and IIIB).

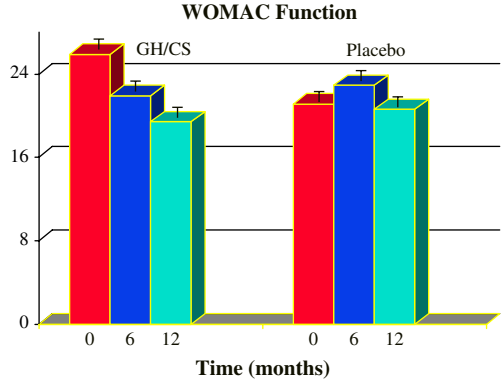

Fig. 2. Mean (SE) WOMAC function at baseline, and 6- and 12-month follow-up. Individual scores on 17 items are added to generate a summary score that can range from 0 to 68. Follow-up values are adjusted for gender, age, baseline value, and BMI. There were no significant differences between the groups at 6- or 12-month follow-up.

Function and pain

During Phase I, pill compliance had no effect on either the GH/CS or placebo group. However, during Phase II, the GH/CS compliant participants had significantly less pain than the non-compliant group ($P = 0.02$) and showed a similar, but non-significant trend in function ($P = 0.06$). Pill compliance had no effect on the placebo group in either function ($P = 0.72$) or pain ($P = 0.71$) at FU12 (Table IV).

The low exercise-compliant placebo group had significantly worse function than either the middle ($P = 0.03$) or high ($P = 0.05$) compliant group (Table V). There was no effect of exercise compliance on function in the GH/CS group ($P = 0.18$). However, exercise compliance had a positive effect on pain in the GH/CS group ($P = 0.04$). GH/CS participants who showed higher compliance had lower mean levels of pain (4.2 ± 0.9) compared to those with low compliance (7.4 ± 0.9).

Table IIIA
Pill compliance by visit and group. A compliant participant was defined as being in the top compliance group (85−100%) during both Phase I (months 0−6) and Phase II (months 7−12) of the study

Group	6-Month (%)	12-Month (%)	Compliant	*N* (%)
GH/CS	0−84.9	0−84.9	No	11 (26)
	0−84.9	85−100	No	0 (0)
	85−100	0−84.9	No	4 (9)
	85−100	85−100	Yes	28 (65)
Placebo	0−84.9	0−84.9	No	13 (31)
	0−84.9	85−100	No	3 (7)
	85−100	0−84.9	No	3 (7)
	85−100	85−100	Yes	23 (55)

Table IIIB
Exercise compliance groups for Phase II (months 7–12). There was no difference in distribution of compliance between the groups

Group	12-Month (%)	*N* (%)
GH/CS	0–69.9	13 (34)
	70–84.9	12 (32)
	85–100	13 (34)
Placebo	0–69.9	14 (38)
	70–84.9	8 (22)
	85–100	15 (41)

Mobility

Pill compliance had no effect on 6-min walk distance at 6-month follow-up for either group (Table IV). However, at 12 months, the compliant GH/CS group walked significantly further on average than the non-compliant group (429.4 m vs 383.8 m, $P = 0.01$). This effect was not apparent in the placebo group ($P = 0.23$) (Table IV).

The low exercise-compliant placebo group had poorer mobility (i.e., walked a significantly shorter distance) than the high ($P = 0.003$) compliant group. Exercise compliance had no statistically significant effect on mobility in the GH/CS group ($P = 0.07$) (Table V).

Strength

There were no significant effects of pill compliance in either the GH/CS or placebo group (Table IV).

The high exercise-compliant GH/CS group was significantly stronger in knee extension strength (mean = 267.4 N) compared to the middle (mean = 182.9 N, $P = 0.01$) and low (mean = 160.7 N, $P = 0.002$) compliant groups (Table V). There was no difference in extension strength in the placebo group ($P = 0.15$). Moreover, exercise compliance had no effect on knee flexion strength.

Balance

There were no positive effects of better pill compliance on mean balance. The only significant effect of pill compliance on mean balance occurred at 6-month follow-up in which the non-compliant GH/CS group had better balance than the compliant cohort ($P = 0.05$) (Table IV).

There was no statistically significant exercise compliance effect on mean balance for either group.

Discussion

Two long-term studies showed significant improvements in self-reported physical function and significantly less disease progression after 3 years of treatment with glucosamine sulfate[2,9]. Michel *et al.*[30] recently showed no joint space loss after 2 years of treatment with CS, but no significant difference in pain and function relative to a placebo. Several meta-analyses concluded that glucosamine and chondroitin reduce pain and may have considerable utility in OA treatment[5–8].

At the conclusion of Phase I, both groups had improved function by 8%. After 12 months, glucosamine/chondroitin combined with exercise for the final 6 months resulted in a 17% improvement from baseline compared to 12% for the placebo group. Despite using appropriate randomization techniques, there was approximately a 20% difference in mean function at baseline. The use of covariance helped to adjust statistically for this difference, but did not account for all of the variance. The lower functional level of the GH/

Table IV
Within group (GH/CS or placebo) effects of pill compliance at 6- (Phase I) and 12-month (Phase II) follow-up on function, pain, 6-min walk, knee strength, and balance (mean + SE)

Outcome	Group	Compliant*	*N*	6-Month†	$P_{6\text{-month}}$	12-Month†	$P_{12\text{-month}}$
Function	GH/CS	No	14	20.2 (1.9)	0.64	21.3 (2.0)	0.06
		Yes	28	21.2 (1.4)		16.9 (1.4)	
	Placebo	No	17	22.1 (1.7)	0.91	20.3 (1.8)	0.72
		Yes	23	22.3 (1.5)		19.4 (1.5)	
Pain	GH/CS	No	14	5.6 (0.7)	0.60	7.3 (0.8)	0.02
		Yes	28	6.0 (0.5)		4.9 (0.6)	
	Placebo	No	17	5.6 (0.6)	0.46	5.1 (0.8)	0.71
		Yes	23	6.2 (0.5)		4.7 (0.6)	
6-min walk (m)	GH/CS	No	15	389.5 (14.0)	0.50	383.8 (14.7)	0.01
		Yes	28	406.3 (9.8)		429.4 (10.3)	
	Placebo	No	19	396.1 (11.7)	0.57	404.6 (12.4)	0.23
		Yes	23	405.2 (11.0)		425.0 (11.5)	
Knee extension strength (N)	GH/CS	No	8	156.8 (28.9)	0.52	200.2 (24.7)	0.86
		Yes	21	179.3 (18.1)		205.3 (15.6)	
	Placebo	No	8	165.8 (28.7)	0.70	184.2 (24.5)	0.28
		Yes	17	214.4 (19.9)		216.2 (17.1)	
Knee flexion strength (N)	GH/CS	No	8	96.9 (13.1)	0.69	98.7 (14.1)	0.97
		Yes	21	103.2 (8.3)		98.1 (8.9)	
	Placebo	No	8	94.8 (13.1)	0.48	115.7 (14.0)	0.67
		Yes	17	106.1 (9.1)		122.9 (9.7)	
Balance (foot length)	GH/CS	No	6	0.57 (0.03)	0.05	0.56 (0.03)	0.40
		Yes	19	0.50 (0.02)		0.52 (0.02)	
	Placebo	No	5	0.54 (0.03)	0.17	0.56 (0.04)	0.52
		Yes	15	0.58 (0.02)		0.59 (0.02)	

*A compliant participant was defined as being in the top compliance group (85–100%) during both Phase I (months 0–6) and Phase II (months 7–12) of the study. †Adjusted for baseline, age and BMI.

Table V
Within group (GH/CS or placebo) effects of exercise compliance on pain, function, 6-min walk, balance, and extension and flexion knee strength (mean + SE). Compliance was divided into high, middle, and low groups

Outcome	Group	Compliance tertile*	*N*	12-Month†	$P_{12\text{-month}}$‡
Function	GH/CS	Low	13	19.1 (2.1)	0.18
		Middle	12	19.7 (2.2)	
		High	13	14.6 (2.1)	
	Placebo	Low	13	23.7 (2.1)	0.05
		Middle	8	16.4 (2.6)	
		High	15	18.0 (2.0)	
Pain	GH/CS	Low	13	7.4 (0.9)	0.04
		Middle	12	5.4 (1.0)	
		High	13	4.2 (0.9)	
	Placebo	Low	13	5.9 (0.9)	0.33
		Middle	8	3.8 (1.2)	
		High	15	4.4 (0.9)	
6-min walk (m)	GH/CS	Low	13	405.5 (14.5)	0.07
		Middle	12	453.8 (15.2)	
		High	13	435.0 (14.3)	
	Placebo	Low	14	395.1 (13.9)	0.01
		Middle	8	422.9 (18.7)	
		High	15	454.5 (13.5)	
Knee extension strength (N)	GH/CS	Low	8	160.7 (24.3)	0.003
		Middle	10	182.9 (22.0)	
		High	10	267.4 (21.8)	
	Placebo	Low	7	166.3 (25.5)	0.15
		Middle	6	217.3 (28.2)	
		High	9	232.7 (22.5)	
Knee flexion strength (N)	GH/CS	Low	8	82.7 (15.9)	0.38
		Middle	10	105.4 (14.5)	
		High	10	110.5 (14.4)	
	Placebo	Low	7	116.4 (16.6)	0.83
		Middle	6	127.6 (18.3)	
		High	9	113.8 (14.8)	
Balance (foot length)	GH/CS	Low	6	0.55 (0.04)	0.27
		Middle	8	0.52 (0.03)	
		High	10	0.59 (0.03)	
	Placebo	Low	4	0.53 (0.04)	0.29
		Middle	6	0.61 (0.04)	
		High	7	0.61 (0.03)	

*Compliance groups: low = 0–68.3%, middle = 69.2–86.9%, and high = 87.2–100%. †Adjusted for baseline, age and BMI. ‡The 12-month *P*-value is an overall comparison between the three groups. When an overall *P*-value was significant, pairwise comparisons were made (see text for details).

CS group at baseline contributed to the large percentage improvement in function without significant between group differences. Based on the OMERACT–OARSI (Outcome measurements in rheumatology–osteoarthritis research society international) set of responder criteria[31] (improvement in both pain and function of $\geq$20%) the GH/CS group showed no clinically important response during Phase I (pill only) or Phase II (pill plus exercise).

Power calculations indicated that we had 80% power to detect an 8.2% difference in mean 6-min walk distance and a 4.6-unit difference in mean WOMAC function (range 0–68) between groups after 12 months. In the ADAPT study, we noted a 5-unit (24%) difference in mean WOMAC function between the healthy lifestyle control group and the exercise plus weight loss group that was statistically and clinically significant[22]. However, in the present study, after 12 months, there was only a 1.2-unit difference between the means of the two groups. Although our study was adequately powered to detect small clinically significant differences, these differences were too small to be detectable and of little clinical interest.

Mean pain scores did not differ between the groups over time; however, there was a threefold reduction in the number of participants who used rescue medication (i.e., acetaminophen) in the GH/CS group compared to the placebo group. Recent evidence from GAIT, a Phase III clinical trial, also found no difference in overall WOMAC pain scores after 24 weeks of receiving either GH, CS, glucosamine plus chondroitin, celecoxib, or a placebo[10]. Clegg *et al.*[10] found a beneficial effect of the combination of glucosamine and chondroitin in a subset analysis of participants with moderate to severe pain. The mild to moderate pain level in our patient population may have contributed to the absence of significant group differences. One of the surprising results

of the GAIT trial was the high placebo effect of approximately 60% in pain. In contrast, our placebo group only had a slight increase in mean pain at 6-month follow-up relative to baseline, from 5.9 to 6.2. Nevertheless, the improvement in the GH/CS group was not sufficient to elicit a significant between-group difference.

Both groups made significant gains in mobility over time (Table II). The addition of exercise to both groups appeared to affect performance similarly. The 6-month follow-up data from the ADAPT trial showed a 9.6% improvement in 6-min walk distance in the exercise only group[22], who attended exercise sessions three times per week at the center. The 5–6% improvement in mobility in the GATES cohort may have been due, in part, to a twice per week rather than a three times per week center-based exercise protocol.

The placebo group made clinically significant gains in mean knee flexion strength from baseline, 23.7 N and 41.8 N during each phase of the study, respectively (Table II). Strength in the GH/CS group, however, remained close to baseline values after 12 months of GH/CS therapy that included 6 months of exercise. Overall, glucosamine/chondroitin therapy, either alone or with exercise, had no effect on knee strength.

Balance data indicated that the placebo group significantly improved relative to the GH/CS group at both 6- and 12-month follow-ups. The placebo group improved balance approximately 10% at 6 months and an additional 2% after 6 months of exercise. While the differences between the groups were statistically different, whether a 10% change in balance in clinically relevant is debatable (Table II).

The lack of a definitive treatment effect with oral glucosamine or chondroitin across studies may also be related to its low bioavailability. Bioavailability is the percentage of drug that enters the blood stream and is available for metabolic use in target tissues (e.g., the joint tissues). Values for acetaminophen and NSAIDs range between 80% and 100%; hence, all or most of these drugs reach the targeted tissues. Oral glucosamine is generally reported as having a bioavailability of approximately 5%[32,33]. Setnikar *et al.*[34] suggested that glucosamine is broken down in the digestive tract, excreted as either carbon dioxide or urea, and readily absorbed by the liver and kidneys. Therefore, only a low percentage of the drug ingested may actually reach the target tissues and evoke metabolic changes in the articular cartilage. Recent evidence provides a slightly more optimistic view. Using a once daily oral administration protocol for 3 consecutive days, Persiani *et al.*[35] estimated that the bioavailability of glucosamine in humans after chronic dosing resulted in maximum plasma concentration levels at steady state (C_{max}) that were higher than previously reported with acute dosing in animal studies. In two unpublished studies, they found similar plasma and synovial fluid concentrations of glucosamine after 14 consecutive days of a regimen of 1500 mg of glucosamine sulfate once-daily, and 27% bioavailability in rats after therapeutic doses of glucosamine sulfate equivalent to 2000 mg for a 65-kg man[36,37].

A potential limitation of the present study was the use of GH. The majority of positive trials has used glucosamine sulfate, not GH; however, to our knowledge there is no direct comparison of the two preparations in human trials to determine if one form is superior to the other. The two products release free glucosamine with glucosamine sulfate releasing a relatively small amount of sulfate (250 mg) relative to the 4.5 g found in normal diets[7,38,39]. Hoffer *et al.*[40] found that there was a significant 14% increase in serum sulfate concentrations 3 h after a 1-g dose of glucosamine sulfate. It is not known if the additional release of sulfate would provide a therapeutic benefit significant enough to result in differences in efficacy.

Oral chondroitin may also have difficulty in reaching the joint tissues. In one study testing GH/CS in dogs, the bioavailability of CS was only 4.9% after a single dose, but showed significant accumulation after 7 consecutive days with over a 200% bioavailability[41]. Providing a single dose to an equine model, Du *et al.*[32] showed a higher bioavailability of low vs high-molecular-weight CS. Cho *et al.*[42] suggested that low-molecular-weight CS is more easily absorbed by the intestinal lining. Baici *et al.*[43] tested oral CS on healthy and arthritic participants and showed that glycosaminoglycan levels in the serum did not significantly change after a single dose. Taken together, these results suggest that a single dose of oral CS may not benefit joint tissues but multiple doses may make chondroitin more bioavailable. Clearly, further studies are needed to determine the actual amounts that reach joint tissues with chronic dosing and the amounts needed in the tissue to achieve a biologic effect.

The possibility that the pain-reducing effects seen in previous studies are due to gastrointestinal and soft tissue absorption of glucosamine and chondroitin instead of biologic effects on joint tissues has also been suggested by previous investigators. Laverty *et al.*[33] and Lippiello *et al.*[44] suggested that the beneficial effects of glucosamine and chondroitin could be due to an overall analgesic effect from absorption in soft tissues, especially in the gastrointestinal track, where extensive first-pass metabolism is evident[32], and not from improvements to the articular cartilage or other joint tissues. The exact mechanism for this effect is not known but is under investigation.

Three long-term RCTs that demonstrated positive results with either glucosamine sulfate or CS used a once-daily medication regimen[2,9,30]. Peak levels of glucosamine occur 2–3 h after ingestion and a 1500-mg dosage provides greater plasma levels of glucosamine than a 750-mg dosage[35]. Overall, these studies suggest that a once-daily dosage of 1500 mg of glucosamine may be more efficacious than other regimens, including the 1500-mg daily regimen used in our study in which participants had the option of once-daily or thrice daily ($3 \times 500/400$ mg) routines.

To determine if there was a dose response to pill compliance, we divided each group into compliant and non-compliant participants. A compliant participant was defined as being in the top compliance group (85–100%) during the first and second 6 months of the study. The pill-compliant GH/CS group showed significantly reduced pain and higher mobility relative to the non-compliant GH/CS group. This trend was not evident in the placebo group.

A strong exercise compliance effect on function and mobility was more apparent in the placebo group, while the high exercise-compliant GH/CS group showed significant improvement in knee extension strength. Hence, high pill compliance tended to be more beneficial for the GH/CS group while high exercise compliance appeared to have some benefit for both groups.

Additional design modifications for future studies should include a once-daily dosage regimen, the use of glucosamine sulfate instead of GH, quantitative or semi-quantitative magnetic resonance imaging (MRI) to document cartilage volume and joint structure[45,46], and a 2×2-factorial design to study the benefits of glucosamine and chondroitin combined with

exercise. Since our study indicated that pill compliance may be critical to the success of the intervention, we recommend that intensive patient education be part of any intervention involving these supplements/drugs. We also agree with Clegg *et al.*[10] that further work regarding the pharmokinetics of glucosamine and chondroitin is required.

Glucosamine and chondroitin have gained wide popularity as alternative treatments for OA. This preliminary study was the first designed to examine the effects of these prescription drugs/nutraceuticals in combination with exercise. The GH/CS group was not superior to the placebo group in function, pain, or mobility after both phases of the intervention (pill only and pill plus exercise). *Post hoc* analysis showed that more pill-compliant participants in the GH/CS group had greater improvements in pain and mobility than less compliant participants; however, caution should be used in interpreting these preliminary data.

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