

## ORIGINAL ARTICLE

# The effect of glucosamine supplementation on people experiencing regular knee pain

R Braham, B Dawson, C Goodman

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See end of article for authors' affiliations

Correspondence to:  
R Braham, Monash University, Department of Epidemiology and Preventive Medicine, Central and Eastern Clinical School, Alfred Hospital, Prahran VIC 3181, Australia; Rebecca.Braham@med.monash.edu.au

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**Objective:** The purpose of this study was to examine the effects of oral glucosamine supplementation on the functional ability and degree of pain felt by individuals who had regular knee pain, most likely due to previous articular cartilage damage, and possibly osteoarthritis.

**Methods:** Subjects were randomly supplemented with either glucosamine (G) (n=24) or placebo (P) (lactose) (n=22) for 12 weeks at a dose of 2000 mg per day. Over this period, four testing sessions were conducted, with changes in knee pain and function assessed by clinical and functional tests, (joint line palpation, a 3 metre "duck walk" and a repeated, walking stair climb), two questionnaires (the Knee Injury and Osteoarthritis Outcome Score (KOOS) and the Knee Pain Scale (KPS)) and participant subjective evaluations.

**Results:** The clinical and functional test scores improved with time (main effects:  $p < 0.05$ ,  $p < 0.01$ ) but there were no significant differences between the two groups. The questionnaire results also recorded a significant main effect for time ( $p < 0.05$ ), but the glucosamine group was found to have significantly better KOOS quality of life scores at week eight and 12 ( $p < 0.05$ ), and lower KPS scores ( $p < 0.05$ ) at week eight than the placebo group. On self report evaluations of changes across the 12 week supplementation period, 88% (n=21) of the glucosamine group reported some degree of improvement in their knee pain versus only 17% (n=3) in the placebo group.

**Conclusions:** These results suggest that glucosamine supplementation can provide some degree of pain relief and improved function in persons who experience regular knee pain, which may be caused by prior cartilage injury and/or osteoarthritis. The trends in the results also suggest that, at a dosage of 2000 mg per day, the majority of improvements are present after eight weeks.

Arthritis is a major cause of limitation in daily functional activities in the general population. It is one of the leading causes of disability in society today and is a major cause of reduced functional mobility, particularly in older people.<sup>1</sup>

The condition of osteoarthritis (OA) is manifested by degeneration of the joints in the body, and is often referred to as "wear and tear" arthritis. Generally, articular cartilage damage is a precursor of osteoarthritis and individuals who suffer from severe cartilage injury usually progress to this degenerative condition. Factors such as aging, obesity, and physical injury all contribute to the degeneration of joint cartilage.<sup>2</sup>

Commonly, analgesics and anti-inflammatory agents are used in the management of OA. Recent studies have also indicated that glucosamine, an amino sugar which is produced by the body, can provide relief from arthritic pain related symptoms.<sup>3–10</sup>

A natural substance found in the body, glucosamine is formed by the combination of glucose and glutamine. It is found primarily in cartilage and plays an important role in its health and resilience. Joint cartilage contains a group of protein molecules called proteoglycans and these proteins make up what is known as the "ground substance" of the cartilage. Many researchers<sup>5, 8, 10–12</sup> believe that joint cartilage is constantly rebuilding itself; such that as old or damaged cartilage degenerates, it is replaced by new healthy cartilage. Glucosamine, in the form of glucosamine sulfate or hydrochloride, has been shown to regenerate cartilage and to exhibit some anti-inflammatory effects.<sup>8, 9, 13</sup>

Essentially, glucosamine is needed to make glucosaminoglycans (GAGs), which are the proteins that bind water in the cartilage matrix. It is a major precursor to the GAGs, which then form the tissue framework that bind colla-

gen. Together, both collagen and GAGs continuously construct and reconstruct cartilage. The production of glucosamine from glucose and glutamine is a rate limiting step in GAG production and therefore in building and rebuilding cartilage.<sup>14</sup> The treatment of joint cartilage damage and more severe OA should focus on strategies to both inhibit cartilage damage and promote cartilage repair. Glucosamine supplementation may be a potential treatment for degenerative joint disease by limiting further degeneration and promoting tissue repair.

Several studies have been conducted examining the effect of glucosamine supplementation on knee pain. Although there are controversies,<sup>15</sup> most studies have supported the use of this supplement in the treatment of osteoarthritis, although they have recently been criticised for insufficient subject numbers,<sup>4, 5, 11</sup> the low dosage and duration of supplementation<sup>3–6, 8, 11</sup> and the lack of inclusion of functional tests.<sup>3–6, 8, 11</sup>

Therefore, the purpose of this study was to examine the effects of 12 weeks of glucosamine supplementation (2000 mg per day) on the functional ability and the degree of pain experienced by individuals who have regular knee pain. If positive effects of glucosamine supplementation are found, then it may be a useful supplemental treatment for chronic knee pain which may be associated with cartilage damage.

## METHODS

The sample comprised 50 volunteers (37 males, 13 females) aged between 20 and 70 years ( $\bar{x}=43y$ ) suffering from regular knee pain of unspecified origin. At the first assessment session, each subject was informed of the experimental protocol, given an information booklet, and signed a declaration of consent before testing began. The experimental protocol was approved by the Human Rights Committee of the University of

Western Australia and all testing was conducted at the Department of Human Movement and Exercise Science at The University of Western Australia.

After advertising for subjects, clinical interviews were conducted to establish whether or not the respondents were suitable for inclusion in the study. This was determined primarily by the severity of knee pain that the subject was suffering from and the limitations that it imposed on their functional mobility, as determined by their responses to both the Knee Pain Scale (KPS)<sup>16</sup> and the Knee Injury and Osteoarthritis Outcome Score (KOOS)<sup>17</sup> questionnaires. As the call for subjects did not specify osteoarthritis, it was important to obtain all relevant information from the subjects about the history of their knee pain, along with any medical diagnoses and radiological assessments. Radiological assessments were not made mandatory in this study due to time and monetary constraints. However, 27 subjects (13 glucosamine, 14 placebo) had had prior medical procedures or assessments which indicated some degree of cartilage damage. It was also important to ensure that all subjects who had regular knee pain were not currently suffering from any other injuries that may have required the use of anti-inflammatory or other medication, or physiotherapy treatment modalities. The selection criteria primarily addressed the severity of knee pain that the individual was suffering from while participating in normal activities of daily living. Subjects who experienced knee pain "more often than not" were included in the study. Each subject, once deemed suitable for the study, was then required to attend four test sessions spaced four weeks apart over the 12 week period. In each of these sessions, both clinical and functional tests were conducted along with completion of the KPS and KOOS. Perceived pain was rated by using a 10 point Likert perceived pain rating scale (0 = no pain; 10 = excruciating pain).

For the duration of the three month supplementation period subjects were instructed to maintain their current, normal exercise habits and refrain from any strenuous exercise on the day before testing sessions. They were also instructed to ingest 2000 mg of either glucosamine hydrochloride or placebo (lactose), in the morning, and record all non steroidal anti-inflammatory drugs (NSAIDs) and prescription medicine taken over the three month period, and complete a daily supplementation record chart, which was received at the initial assessment session.

A double blind experimental design was employed and subjects were randomly assigned to either the placebo (P) or glucosamine (G) group based on the order in which they attended their first assessment session. As far as possible, participants were tested at the same time and on the same day of the week to minimise any variations which may occur as a result of testing at different times or on different days.

At each of the four assessment sessions, subjects were asked to complete the following tasks to assess the severity of their current knee pain the KPS and KOOS questionnaires, joint line palpation (conducted by the experimenter) of both knees, "duck walk" for 3 m and a stair climb of 32 steps (16 up and 16 down) repeated up to five times.

Both the KPS and KOOS questionnaires were used as they have proven to be valid and reliable instruments in measuring the severity of knee pain.<sup>16 17</sup>

The joint line palpation was used as a means of measuring the pain on palpation of the articular or meniscal cartilage. The "duck walk" over a 3 m set distance followed the joint line palpation. The same 3 m floor area was used at all test sessions. The "duck walk" was used as a component of the functional tests because it allows maximal load to be placed on the knee joint and results in compression of the menisci and joint surfaces.

The stair climb involved climbing 32 steps (16 up and 16 down) repeatedly for up to five times, for a total of 160 steps. Subjects were not permitted to use hand rails when ascending

**Table 1** Characteristics of the patients and their knee pain history ( $\bar{x}$  (SD))

	Glucosamine group	Placebo group
No of patients	24	22
Male	17	16
Female	7	6
Age (y)	41.6 (12.5)	43.8 (10.4)
Male	40.0 (13.4)	45.0 (7.7)
Female	45.6 (9.6)	40.5 (16.4)
Age classes:		
<35 y	9	5
36–50 y	8	10
51–70 y	7	7
Localisation of pain		
Left	11	13
Right	7	7
Bilateral	6	2
Duration of symptoms		
Less than 1 year	3	0
1–5 y	5	3
6–10 y	9	4
>10 y	7	15
	$\bar{x} = 10.3 \text{ y } (\pm 9.4)$	$\bar{x} = 15.9 \text{ y } (\pm 8.6)$

or descending the stairs. The same set of stairs was used at each session. This functional test was used to assess knee joint pain, as climbing stairs loads the knee joint both concentrically and eccentrically, and often elicits knee pain. Subjects were asked to rate their perceived pain after each test using the 10 point Likert scale on the injured knee.

## STATISTICAL ANALYSIS

A two way ANOVA with repeated measures was used to analyse the data (SPSS for Windows, version 8.0). Where appropriate, post hoc tests (paired *t* tests) were used to determine the location of any significant differences. Significance was accepted at  $p \leq 0.05$ . Descriptive statistics were also used to gain a general perspective of the data, to record each group's improvement on functional and clinical tests along and pain ratings, over the three month period of supplementation.

## RESULTS

### Subjects

Of the 50 subjects who commenced the trial, 24 subjects in the G group and 22 subjects in the P group completed the study according to the experimental protocol. The remaining 4 participants did not complete the study as they required surgery on their knees during the three month period. Table 1 presents the characteristics of the subjects and their knee pain history. Importantly, while the subjects were instructed to maintain their usual exercise routines over the 12 week period of the study, none was forced to consistently reduce his or her exercise levels over the time by increases in knee pain.

### Compliance

Each of the subjects was instructed to report his or her supplement dosage compliance over the three month testing period. The required 168 g of supplement was taken by 98% of the subjects. Two subjects missed three and six days respectively due to reasons beyond their control. The use of NSAIDs were not encouraged over the testing period, however, four subjects felt the necessity to take these drugs at certain stages of the study. One subject in the glucosamine group continued to supplement with NSAIDs for the duration of the study. The remaining three subjects who supplemented with NSAIDs did so at various stages throughout the three months, and the average duration of supplementation was five days. However, no subject supplemented with NSAIDs during their

**Table 2** Side effects reported by the patients during the study

Side effect	Glucosamine group	Placebo group
Nausea/vomiting	1 (1)	2 (7–14)
Gastrointestinal upset/cramps	4 (7–28)	3 (14–21)
Headache	2 (7–14)	4 (5–21)
Bloating	1 (28)	1 (7)
Dry mouth	2 (28)	0
Tenderness in knee	1 (28)	0
<b>Total</b>	<b>11</b>	<b>10</b>

The number of patients with symptoms are reported. In brackets is the duration of the side effect (in days) as reported by the subjects (some subjects reported more than one of the listed side effects at the same time).

assessment weeks, other than the subject who supplemented continually with NSAIDs. No other complementary medicines or therapies were used during the course of the study.

**Side effects**

Table 2 summarises the patients who reported minor side effects during the supplementation period.

Fifteen subjects (33%) presented with mild side effects over the duration of the study, however, none found them severe enough to warrant withdrawal from the study. The side effects were evenly distributed between the two groups, with 11 symptoms reported by the G group and 10 symptoms reported by the P group. The side effects experienced were generally short lived, with the average duration being seven days. Some subjects suffered more than one side effect and this was more common in the placebo group.

**Clinical and functional tests**

**Joint line palpation (JLP)**

A significant main effect for time ( $p < 0.05$ ) was found to exist, with pain ratings decreasing over the 12 weeks, though there was no significant group or group by time differences found.

**“Duck Walk”**

Subjects were not asked to attempt the duck walk unless they were able to complete a full squat, and this was achieved at each assessment by 22 subjects in each group. There was no change in the distance covered in the duck walk for any of the subjects in the P group, but four (16%) of the G group showed an increase in distance (2.1–3 m) covered over the three month period.

Subjects rated their knee pain after the completion of the 3 m duck walk or at the best position that they could achieve in the squat. A significant group main effect was found for knee pain rating, with the G group reporting less pain than the P group at all four test sessions. A significant main effect for time was also found for knee pain rating, as both groups improved their pain ratings over the 12 weeks, but no significant group by time interaction was evident.

**Stair climb**

All subjects from both groups were able to complete successfully the required 160 steps at each assessment period. Significant group ( $p = 0.002$ ) and time ( $p = 0.030$ ) main effects were found, with the G group having a lower average pain rating at each assessment session, and both groups improving over the 12 weeks. However, there was no significant interaction between groups over time ( $p = 0.681$ ).

**Knee pain scale (KPS)**

The mean scores of the KPS for the two groups at the four assessment sessions are presented in table 3. Both groups improved (decreased) their KPS responses over the three

**Table 3** Mean (SD) scores for the Knee Pain Scale (the lower the scores the better) for the glucosamine and placebo groups over the three month supplementation period

Time	Glucosamine (n=24)	Placebo (n=22)
Week 0 <sup>A B C</sup>	30 (10)	34 (8)
Week 4 <sup>A D E</sup>	27 (10)	31 (10)
Week 8 <sup>B D</sup>	23* (8)	31 (10)
Week 12 <sup>C E</sup>	24 (8)	28 (11)

Identical superscripts indicate a significant main effect for time at  $p < 0.05$ .

\*Denotes significant difference between groups at  $p < 0.05$ .

month period (main effect for time;  $p = 0.00$ ), but at week eight the G group scores were significantly lower ( $p = 0.004$ ) than the P group scores.

**Knee injury and osteoarthritis outcome score (KOOS)**

There are five sections of the KOOS, and the raw scores of each were standardised before being analysed. A total KOOS score was calculated by summing the raw scores of each section which was then also standardised as per the methods of Roos et al.<sup>17</sup> The mean  $\pm$ SD scores of all sections of the KOOS are presented in table 4.

Standardised scores for each of these sections ranged from 0–80, with higher scores representing lower pain levels and a better KOOS response. A significant time effect was found to exist for all five sections in the questionnaire (with  $p$  values ranging from 0.000–0.019) as both groups improved their scores over the 12 weeks. Significant group differences were found for pain ( $p = 0.025$ ) and activities of daily living ( $p = 0.045$ ) where the G group had higher scores (indicative of lower pain levels) at each assessment. A significant interaction between groups over time was found for knee related quality of life ( $p = 0.038$ ) where the G group had a higher average score at week eight and week 12.

**Changes in perceived pain**

Changes in perceived pain were assessed based on each individual subjects’ self reported perception of improvement over the supplementation period. The majority (88%) of supplemented subjects felt that their knee pain had improved by some degree over the three months, while only 12% felt that there was no change in symptoms. In comparison, 83% of the P group reported no change, with only 17% reporting any improvement in symptoms. Only three subjects in the G group reported no change at any of the assessment sessions. In comparison, 19 subjects in the P group reported no change in perceived pain at each of the three assessment sessions.

It was apparent that the majority of self reported changes in the G group occurred between week four and eight after supplementation commenced. At week four, 36% of subjects reported some degree of pain relief, at week eight this had increased to 68%, and at week 12 a further increase was evident, with 88% recording some improvement in pain levels. Only 17% of the P group reported pain improvements and the majority of these occurred by week eight.

**DISCUSSION**

Our study differed from previous investigations in that, firstly, the supplementation of glucosamine was for a period of three months, whereas subjects have usually only been supplemented with glucosamine for between four and eight weeks.<sup>3–6 8 11 15</sup> Only one investigation has used a longer supplementation period<sup>18</sup> (five months) and while the results were generally positive, no control group was used in the experimental design, limiting the interpretation of the data. The results of these earlier studies did also suggest that a

**Table 4** Mean (SD) standardised KOOS scores over the testing period for the glucosamine (G) and placebo (P) group

Section of KOOS	Week 0		Week 4		Week 8		Week 12	
	G (n=25)	P (n=23)	G (n=25)	P (n=22)	G (n=25)	P (n=23)	G (n=24)	P (n=22)
Pain <sup>A B</sup>	55 (11)	49 (15)	57 (11)	54 (13)	62 (10)	52 (14)	60 (11)	54 (14)
Symptoms <sup>A</sup>	48 (12)	41 (12)	52 (14)	47 (14)	55 (14)	48 (16)	54 (14)	50 (15)
Activities of daily living <sup>A B</sup>	61 (11)	56 (14)	64 (12)	59 (13)	68 (10)	58 (15)	67 (11)	62 (15)
Sport/recreation <sup>A</sup>	40 (21)	46 (23)	50 (19)	52 (22)	55 (19)	55 (22)	53 (18)	46 (21)
Knee related quality of life <sup>A C</sup>	34 (15)	27 (13)	34 (17)	30 (13)	40* (17)	29 (14)	42* (16)	32 (15)
Total KOOS score <sup>A</sup>	53 (11)	49 (10)	56 (11)	53 (11)	61 (11)	52 (12)	60 (11)	54 (14)

<sup>A</sup>Significant main time effect at  $p < 0.05$ .

<sup>B</sup>Significant group main effect at  $p < 0.05$ .

<sup>C</sup>Significant interaction at  $p < 0.05$ .

\*Significant group difference at  $p < 0.05$ .

longer time frame of supplementation may prove to be more beneficial.<sup>11</sup> Secondly, our study also incorporated some simple clinical and functional tests (besides subjective or self report assessments) to evaluate improvements in pain with supplementation, as these types of test have not been used as part of the assessment procedures in previous studies. Thirdly, the supplementation amount chosen for use in our study was 2000 mg, larger than the majority of previous glucosamine studies. Earlier studies have used supplementation levels of between 450 mg and 3000 mg daily, and it was reported that a higher dosage of supplementation is well tolerated by subjects.<sup>19</sup>

Qualitatively, our study supported the findings of many reports<sup>3-6 8 11 18 20</sup> which have suggested that glucosamine supplementation provides some degree of pain relief and improved mobility to subjects who experience regular knee pain which may be due to cartilage damage and possibly OA. Subjectively, 88% of G subjects (and only 17% of P subjects) self reported pain and mobility improvements over the supplementation period. These self reported changes also indicated that the majority of benefits occurred between week four and eight of supplementation, as reported by several other studies.<sup>3-6 8 11</sup>

In our study we incorporated some simple functional and clinical tests, in order to provide some more objective data on the effects of the G supplementation. Most previous studies have only reported on the subjective perceptions of pain of the subjects, although some<sup>11 15</sup> have recorded pain ratings after walking. However, the joint line palpation, "duck walk", and stair climb results did not produce any significant group interactions across the 12 week supplementation period, therefore no evidence of a positive effect of the glucosamine on the functional ability and palpated pain responses was provided by these tests. Whether the tests chosen here are sufficiently discriminating to isolate any effects that glucosamine may have on knee cartilage integrity and pain on loading is not known, and awaits further research—perhaps in conjunction with radiological assessment of cartilage integrity before and after a period of glucosamine supplementation. Future research should also consider the assessment of pain and functional ability on consecutive days (rather than just on a single day) at regular intervals over a supplementation period, as, in many of our subjects, pain did not manifest immediately after exertion (such as the "duck walk" or stair climb), but was present several hours later or on the next day. This experimental design may assist in the gathering of more objective data about the effects of glucosamine supplementation on knee pain which may be associated with OA. Nevertheless, the KPS and KOOS scores did show some differences between the G and P groups, with the G subjects reporting lower KPS scores at week eight and higher KOOS knee related quality of life scores at weeks eight and 12. These results may reflect more general improvements in pain and functional ability in the G group over the whole of the supple-

mentation period, rather than any acute effects noted during or after the week eight and 12 assessment sessions which were only conducted on a single day. Our study also used a large (2000 mg) daily dose of glucosamine and a lengthy (12 weeks) period of supplementation, in contrast to other research,<sup>3-6 8 11</sup> although these studies have also reported some (although not comprehensive) positive effects of glucosamine supplementation on knee pain and arthritis symptoms, when compared to placebo treatment. In contrast, Rindone *et al*<sup>15</sup> recently reported that glucosamine supplementation was no more effective than placebo in treating knee OA, however, their daily supplementation was only 500 mg and treatment was only undertaken for two months. The low daily dose and shorter period of supplementation may explain their lack of positive findings, as theirs is virtually the only study to record neutral or negative results in respect of glucosamine supplementation and knee pain. Their G subjects also had confirmed (by radiographic analysis) OA in the knee, and had had the disease for an average (SD) of 12 (10) years which is slightly longer than the knee pain history in our subjects (10.3 (9.4) years). Because of financial constraints, our subjects were not all confirmed radiologically as having OA in their knees (although this was suspected clinically) before being accepted into the study, and our eventual P subjects (after random assignment to treatment groups) were found to have a longer history of knee pain (15.9 (8.6) years) than our G subjects. These factors may have had some influence on the results recorded here, as it is possible that the longer the time that an individual has been suffering with knee pain and/or OA the less effect glucosamine supplementation (or any form of treatment) is likely to have within a given time frame.<sup>15</sup> Also, as the majority of our subjects remained active over the supplementation period, it is important to note that none (from either the G or P group) were forced to consistently reduce their exercise levels over the three months. This indicates that neither group suffered an increase in knee pain, perhaps caused by their regular exercise habits, over the 12 weeks, which is another factor which potentially could have influenced the results.

In conclusion, this study supports the findings of the majority of similar studies conducted into glucosamine supplementation, showing that it can provide some pain relief and self reported improvements in functional ability in subjects who suffer from regular knee pain which may be due to cartilage damage and possible OA. Subjectively, all of the five different variables assessed in this study showed some evidence of a greater degree of improvement in the G subjects than the P subjects over the 12 week supplementation period. Though there were only a few significant results found, 88% of G subjects self reported pain relief associated with its use, as opposed to only 17% of P subjects. Future research should include radiological assessment by magnetic resonance imaging both before and after supplementation, in order to provide objective evidence of any change in cartilage integrity after glucosamine treatment. Also functional tests of the type



### Take home message

Glucosamine supplementation (2000 mg per day, for 12 weeks) may result in decreased pain ratings and self reported improvements in functional ability of subjects suffering from chronic knee pain.

trials here should be continued, with pain and functional ability assessments being made on consecutive days, as pain from exertion and loading of the cartilage may not manifest immediately.

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### Authors' affiliations

**R Braham, B Dawson, C Goodman**, Department of Human Movement and Exercise Science, University of Western Australia, Crawley, Western Australia 6009

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### COMMENTARY

This was a well conducted study using a placebo and experimental dosage of glucosamine in a group of 46 subjects for a period of three months. Knee pain was assessed by both clinical and functional tests as well as using two knee Injury/ Knee pain questionnaires.

Although there were no differences in the functional and clinical tests between the two groups, the glucosamine group reported better knee pain scores after testing, as well as better quality of life scores at weeks eight and twelve. In line with some of the previous work in this area (see their references 3 and 8) the authors have suggested, rightly so in my opinion, that glucosamine treatment will have a beneficial effect for patients suffering with knee pain.

**L McNaughton**

Exercise Physiologist and Director of Postgraduate Studies,  
University of Bath, Claverton Down, Bath BA2 7AY, UK;  
l.mcnaughton@bath.ac.uk