

## ORIGINAL ARTICLE

# Predictors of symptomatic response to glucosamine in knee osteoarthritis: an exploratory study

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**Objective:** To evaluate whether patient characteristics and/or radiographic disease patterns predict symptomatic response to treatment with glucosamine in osteoarthritis (OA) of the knee.

**Design:** Exploratory prospective correlational study.

**Setting:** Institutional.

**Patients:** 39 participants with chronic knee pain from the local community.

**Interventions:** Glucosamine sulphate (1.5 g/day) for 12 weeks.

**Main outcome measures:** Pain and physical function were assessed with visual analogue scales (VASs) and participant-perceived global change scores (GCSs). Regression modelling evaluated the relationship between treatment outcome and age, body mass index (BMI), pain and function self-efficacy and presence/absence of osteophytes in the medial and lateral tibiofemoral joint (TFJ) and patellofemoral joint (PFJ) compartments.

**Results:** 13 (33%) participants were men. The mean (SD) age and BMI were 53.6 (13.1) years and 27.9 (4.6) kg/m<sup>2</sup>, respectively. 13 (33%), 19 (49%) and 24 (62%) participants had medial TFJ, lateral TFJ and PFJ osteophytes, respectively. Glucosamine significantly improved pain (mean change on VAS = -1.4, 95% CI -0.6 to -2.2; p=0.002) and activity restriction (-1.9, 95% CI -1.0 to -2.8; p<0.001). At 12 weeks, 30 (77%) and 27 (69%) participants reported improvement in pain and physical function, respectively. Regression modelling showed that no evaluated variables predicted change in pain on VAS. Decreased function self-efficacy, presence of PFJ osteophytes and absence of medial TFJ osteophytes predicted functional improvement on VAS. BMI, pain self-efficacy and function self-efficacy predicted improvement in pain by GCS.

**Conclusions:** Although glucosamine significantly improved symptoms, most of the variance in outcome at 12 weeks was unexplained by the predictors evaluated. However, glucosamine may be more effective at improving symptoms in patients with knee OA who have a lower BMI, PFJ osteophytes and lower functional self-efficacy.

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Osteoarthritis (OA) is the most common form of arthritis, and is a leading cause of physical disability, increased healthcare usage and impaired quality of life.<sup>1,2</sup> The knee is the principal large joint affected by OA<sup>3</sup>; symptomatic OA of the knee affects 6% of the US population aged >30 years.<sup>4</sup> Conservative treatments for knee OA are critical as there is no cure for the disease. Current medical treatment options are limited. The most significant symptom of knee OA is pain.<sup>3</sup> Unfortunately, the pharmacological treatments designed to relieve pain, such as non-steroidal anti-inflammatory drugs, cyclo-oxygenase-2 inhibitors and analgesics have considerable side effects which increase the mortality and morbidity associated with OA.<sup>6–9</sup> Consequently, clinical guidelines recommend conservative non-pharmacological strategies as the preferred treatment for knee OA.<sup>10,11</sup>

Glucosamine is a hexosamine sugar and is a basic building block in the biosynthesis of glycosaminoglycans, which, in combination with collagen, forms articular cartilage.<sup>12</sup> As such, it is hypothesised that glucosamine may beneficially modify the natural course of OA, alleviating symptoms and possibly slowing the progression of disease. Glucosamine has therefore been used in the treatment of OA for many years. In the last 20 years, the scientific evidence to support its use has been increasing, with systematic reviews reporting favourable results for glucosamine in the treatment of knee OA.<sup>10,13–15</sup> These reviews included mainly short-term studies of up to 3 months duration but also two long-term studies<sup>16,17</sup> of over 3 years each. These long-term studies concluded that glucosamine improves pain and function and is extremely safe, and also that

it has disease-modifying effects, which retard the progression of knee OA. However, the most recent Cochrane Review (updated in 2005), which analysed the newest and highest quality studies available, concluded that glucosamine offers no benefit over placebo in the relief of knee OA pain.<sup>18</sup> Accordingly, the authors recommended future research to determine whether glucosamine is effective for all patients with knee OA, and what patient-specific characteristics may influence the outcome. Such a recommendation has also been made by the European League Against Rheumatism<sup>10</sup> as little is known about clinical predictors of response to pharmacological and non-pharmacological interventions in OA.

To date, no study has specifically evaluated factors that may influence response to glucosamine in knee OA. One subanalysis<sup>19</sup> identified a trend for patients with the least severe radiographic medial tibiofemoral joint (TFJ) OA to demonstrate less joint-space narrowing over 3 years with glucosamine than with placebo, a relationship not evident in patients with more severe disease. It is possible that other factors, such as radiographic compartmental presentation of disease- or patient-specific characteristics, may also mediate response to glucosamine. The aim of this study was to evaluate whether characteristics specific to the patient and/or patterns of radiographic disease presentation could predict symptomatic response to treatment with glucosamine.

**Abbreviations:** BMI, body mass index; GCS, global change score; OA, osteoarthritis; PFJ, patellofemoral joint; TFJ, tibiofemoral joint; VAS, visual analogue scale

## METHODS

### Experimental design

A prospective correlational study of preintervention and postintervention was conducted. The Radiation Safety Program, Department of Human Services, Melbourne, Victoria, Australia, and the Human Research Ethics Committee, University of Melbourne, Melbourne, Victoria, Australia, approved the study. All participants provided written informed consent.

### Inclusion and exclusion criteria

A total of 45 participants were recruited from the local community via newspaper advertisements. Inclusion criteria were knee pain on most days of each week for at least 3 months and an average knee pain score of  $>3$  on an 11-point numerical pain scale. Exclusion criteria were: age  $<30$  years; evidence of a soft tissue diagnosis, inflammatory diagnosis, significant intra-articular derangement, significant lumbar spine arthropathy, hip/ankle arthropathy, or other neuromuscular conditions affecting the ipsilateral leg, or knee surgery, intra-articular corticosteroid/hyaluronic acid; traumatic knee injury and glucosamine supplementation, within the previous 6 months; early morning stiffness for  $>30$  min in the affected knee; allergies to shell fish. Exclusion diagnoses were assessed clinically.

### Intervention

Glucosamine sulphate at a dosage of 1.5 g/day was used, as this is the most widely used compound and dosage.<sup>10</sup> An intervention period of 12 weeks was used, as numerous studies have demonstrated beneficial effects of glucosamine sulphate on pain and function within this timescale.<sup>20–23</sup> Participants were instructed to take one capsule (Mayne Consumer Products, Mayne, Australia) containing 750 mg of glucosamine sulphate twice daily.

Stable doses of simple analgesia or non-steroidal anti-inflammatory drugs were permitted during the study.

### Assessment of response to treatment

Participants underwent assessment at baseline and after intervention at 12 weeks. Outcome measures used to determine response to glucosamine were:

- Visual analogue scale (VAS) to assess pain on movement, and restriction in activities of daily living, over the past week. The VAS has been shown to be valid in the subjective assessment of knee complaints.<sup>24</sup> Possible scores ranged from 0 to 10, with 10 representing worst pain/most activity restriction.
- Participant-perceived global change score (GCS) in each of knee pain and physical function, since commencing treatment. Participants were asked to rate their improvement on a five-point scale. Participants who indicated that their symptoms were much worse, slightly worse or unchanged were classified as non-improvers (and scored 0), while those who reported symptoms as slightly better or much better were classified as improvers (and scored 1).

### Predictors of response to treatment

The following potential predictors of response to glucosamine were evaluated:

- Participant's age, in years.
- Body mass index (BMI), in  $\text{kg}/\text{m}^2$ .
- Self-efficacy. The pain subscale and the function subscale of the Arthritis Self-Efficacy Scale were used. Participants indicated their certainty to perform particular tasks (relating

to pain management and 9 relating to function) on a 10-point scale, ranging from very uncertain (score of 1) to very certain (score of 10). For each subscale, the mean of the respective items was taken as the total score.

- Compartmental patterns of osteophytosis as seen on knee radiographs. Views, taken at baseline, included a posterior–anterior semiflexed weight-bearing view of the TFJ as well as a skyline view of the patellofemoral joint (PFJ). Each knee joint compartment was evaluated for the presence of osteophytes—namely, the medial TFJ, the lateral TFJ and the PFJ. Radiographs were evaluated by ANB, a rheumatologist of 6-years experience. Each of the three compartments was given a score of either 0 (indicating no osteophytes) or 1 (osteophytes present). Osteophytes were the only radiographic parameter assessed, as this is deemed the most critical by the American College of Rheumatology in diagnosing OA. In our cohort of patients with  $>3$  months of knee pain and  $<30$  min early morning stiffness, the presence of osteophytes on an individual's x ray confirmed the diagnosis of OA as per the criteria of the American College of Rheumatology.

### Data analysis

Data were analysed using SPSS version 14.0 for Windows and an  $\alpha$  level of 0.05 was used. The VASs at baseline and 12 weeks were compared with paired t tests. Change in VASs were determined by subtracting the score obtained at baseline from the score obtained at 12 weeks, such that negative scores indicated improvement in VAS parameters. To determine predictors of outcome at 12 weeks, regression analyses were performed. Independent variables entered into the model included age, BMI, pain self-efficacy, function self-efficacy and osteophyte score for each of the PFJ, medial TFJ and lateral TFJ. For the continuous dependent variables of change in VAS measures, backward stepwise elimination linear regression models were used (criteria for entry  $p<0.05$  and removal  $p<0.1$ ). For the categorical dependent variables of participant-perceived change in pain and physical function, backward stepwise logistic regression models were used (criteria for entry  $p<0.05$  and removal  $p<0.1$ ).

## RESULTS

### Cohort characteristics

Complete datasets were obtained on 39 people (33% men (13/39)). Mean (SD) age and BMI of participants were 53.6 (13.1) years and 27.9 (4.6)  $\text{kg}/\text{m}^2$ , respectively. Mean (SD) self-efficacy scores obtained for pain and physical function were 5.84 (1.84) and 8.17 (1.69), respectively. In all, 13 (33%), 19 (49%) and 24 (62%) participants demonstrated osteophytes in the medial TFJ, lateral TFJ and PFJ, respectively.

Six participants failed to complete the trial: two dropped out because of pregnancy and knee arthroscopy, respectively, two subjects forgot to take the glucosamine on holiday with them, one had gastrointestinal side effects and one failed to attend follow-up.

### Effect of glucosamine

Treatment with glucosamine significantly improved VAS scores for pain and activity restriction across the cohort. Pain on movement improved from a mean (SD) score of 4.6 (1.7) at baseline to 3.3 (2.3) at 12 weeks (mean change =  $-1.4$ , 95% CI  $-0.6$  to  $-2.2$ ;  $p=0.002$ ), and restriction in daily activities improved from 4.6 (2.3) to 2.7 (2.3) at 12 weeks ( $-1.9$ , 95% CI  $-1.0$  to  $-2.8$ ;  $p<0.001$ ). At the completion of treatment, 30 (77%) and 27 (69%) participants reported improvement in pain

and physical function, respectively, according to the patient-perceived GCS.

### Predictors of response

Inclusion of all variables in the regression model accounted for 15.7% of the variance in change in VAS scores for pain on movement at 12 weeks. However, all of the seven selected dependent variables were then excluded from the model, and thus they could not explain any of the changes in this outcome measure. Inclusion of all variables accounted for 26.1% of the variance in change in VAS activity restriction. The final prediction model ( $F = 6.700$ ,  $p = 0.001$ ) included only function self-efficacy ( $\beta$  (regression coefficient) = 0.639,  $p < 0.001$ ), PFJ osteophytes ( $\beta = -0.409$ ,  $p = 0.017$ ) and medial TFJ osteophytes ( $\beta = 0.579$ ,  $p = 0.005$ ), giving an adjusted  $R^2$  of 0.310. Thus, this model accounted for 31% of the variance in change in activity restriction after 12 weeks of treatment with glucosamine. For the dependent variable of improvement in pain, logistic regression modelling revealed that BMI, pain and function self-efficacy, PFJ osteophytes and lateral TFJ osteophytes were predictive of outcome, but the last two were not significant (table 1). An increase in BMI and function self-efficacy was associated with reduced odds of reporting improvement in pain, while an increase in pain self-efficacy was associated with increased odds of reporting improvement in pain. For the dependent variable of improvement in physical function, logistic regression modelling revealed only age and BMI to be predictive of outcome, and these were not significant (table 1).

### DISCUSSION

The efficacy of glucosamine for the management of knee OA is controversial. Although many studies have demonstrated the beneficial effects of glucosamine on symptoms and joint structure in patients with knee OA,<sup>16 17 25–27</sup> the most recent Cochrane Review,<sup>18</sup> which evaluated newer and higher quality clinical trials than an earlier review,<sup>15</sup> concluded that glucosamine has no greater effect on pain than placebo. Beneficial effects of glucosamine on pain were evident only when lower quality clinical trials were included in the analysis or when only studies evaluating the Rotta (Rotta Pharmaceuticals, Wall, New Jersey, USA) brand of glucosamine were evaluated. The effect of glucosamine on function depended on the type of outcome scale utilised. Although many reasons may explain the inconsistency of results in the literature, one explanation may be that glucosamine does not have a systematic effect in all patients with knee OA, such that only certain subgroups of patients respond to treatment. The aim of this study was to identify whether characteristics specific to the patient and/or patterns of radiographic disease presentation could predict symptomatic response to treatment with glucosamine. Although glucosamine was effective at improving symptoms

in our cohort, most of the variance in outcome at 12 weeks was unexplained by the predictors evaluated. Furthermore, factors predictive of response to treatment varied according to the outcome measure used.

Assessment of change in both pain and physical function are considered integral to the evaluation of treatment efficacy in patients with knee OA,<sup>28 29</sup> which is why we selected these parameters to assess response to glucosamine in this study. There are many measurement tools available to evaluate changes in knee pain and physical function, and these could be performance based, patient rated or investigator rated. We selected the VAS because of its simplicity to administer and its wide application in the knee OA literature. We also chose to record the participant-perceived rating of change with treatment, as patient-reported GCSs, along with pain and physical function, are considered a core domain to evaluate in the clinical trials of OA.<sup>28</sup> In our cohort, knee pain on VAS improved by 30% and activity restriction on VAS improved by 40% after 12 weeks of treatment with glucosamine. These improvements are of a similar magnitude to those reported by others.<sup>16 27</sup> As it was not our intention to evaluate efficacy, our study design did not incorporate a control group and, thus, it is not possible to determine how much of the positive response can be attributed to a biological effect of glucosamine or a placebo effect. It is unlikely that the improvements observed over the 12-week period are due to the natural history of the disease, as the participants had had chronic symptoms for a mean of 9.5 years, and thus were unlikely to demonstrate such improvement naturally.

It was hypothesised that patient-specific characteristics—namely, age, BMI and self-efficacy—would mediate symptomatic response to glucosamine. These factors have been identified as determinants of pain severity and physical function in knee OA<sup>30–32</sup> and have also been shown to influence the outcome with other conservative interventions for this condition such as laterally wedged insoles and exercise therapy.<sup>33–35</sup> A subanalysis in a clinical trial of glucosamine<sup>19</sup> has suggested that radiographic disease presentation may mediate its influence on joint structure over time. As knee OA manifests in a variety of radiographic patterns,<sup>36</sup> and evidence indicates that the PFJ could be a more potent source of symptoms than other compartments,<sup>37–39</sup> it was also hypothesised that response to glucosamine would be influenced by radiographic compartmental presentation of disease.

None of the parameters evaluated in this study predicted change in pain on the VAS after treatment with glucosamine. In contrast, BMI, pain self-efficacy and function self-efficacy were significant predictors of improvement in pain on the participant-perceived GCS. These results highlight the complex multifactorial nature of the pain experience in patients with knee OA and reinforce the knowledge that different instruments for measuring pain capture different domains of the pain

**Table 1** Results of logistic regression modelling for improvement in pain and physical function, as recorded on the participant-perceived rating of change scales

Dependent variable	Predictors	B	p Value	OR	95% CI
Improved pain*	BMI	-0.237	0.04	0.79	0.63 to 0.99
	Pain self-efficacy	0.832	0.03	2.30	1.08 to 4.87
	Function self-efficacy	-1.336	0.03	0.26	0.08 to 0.85
	PFJ osteophytes†	2.442	0.10	11.50	0.63 to 208.71
	Lateral TFJ osteophytes†	-3.521	0.06	0.03	<0.01 to 1.17
Improved function*	Age	0.063	0.08	1.07	0.99 to 1.14
	BMI	-0.169	0.07	0.84	0.71 to 1.01

BMI, body mass index; PFJ, patellofemoral joint; TFJ, tibiofemoral joint.

\*0, not improved; 1, improved.

†0, absent; 1, present.

### What is already known on this topic

- Glucosamine is a commonly used food supplement in the general and sporting population.
- It is taken for knee pain and osteoarthritis (OA).
- There is conflicting evidence about its efficacy in knee OA.
- There is no significant evidence for its use in other forms of OA.

### What this study adds

- It clarifies the conflicting evidence for the efficacy of glucosamine in knee osteoarthritis (OA).
- It generates the hypothesis that only some subgroups of patients will respond to glucosamine.
- It suggests that glucosamine may be more effective at improving symptoms in patients with knee OA who have a lower body mass index, patellofemoral joint osteophytes and lower functional self-efficacy.

process. The lack of a clear and consistent significant association between radiographic disease presentation and changes in pain supports other studies demonstrating a generally weak relationship between structural changes and symptoms of the disease.<sup>40–42</sup> Decreased BMI, increased pain self-efficacy and decreased function self-efficacy at baseline were all associated with a greater likelihood of reporting improvement in pain at 12 weeks. The reasons underlying these associations are not clear from this study. However, one possible explanation for the association of response with decreased BMI is that increased BMI is a predictor of incidence and progression of radiographic OA.<sup>43–46</sup> Therefore, we hypothesised that individuals with a high BMI would be less likely to have a positive response to glucosamine. This is based on the knowledge that glucosamine only has a moderate effect on outcome of patients with knee OA,<sup>10 13</sup> so if any particular individual has known risk factors for the progression of OA in the knee, such as increased BMI, then this risk factor could outweigh the potential beneficial effects of glucosamine.

Several factors were associated with the improvement in function observed on the VAS after treatment with glucosamine and these included reduced function self-efficacy at baseline, the presence of PFJ osteophytes and the absence of medial TFJ osteophytes. Together, these variables accounted for a third of the variance in outcome, suggesting that factors other than those measured in this study were responsible for most of the improvement on this outcome measure. These results suggest that patients with PFJ disease, rather than TFJ involvement, are more likely to demonstrate functional improvement with glucosamine. It is unclear why this is so, but may be related to differences in biochemical and mechanical properties between patella cartilage and that of the tibia and femur.<sup>47–49</sup> Similar to our findings with regard to pain, predictors of change in physical function were not consistent across measurement tools. Logistic regression modelling revealed age and BMI as non-significant predictors of participant-perceived change in function.

Findings from this study suggest that glucosamine may be more effective at improving symptoms in patients with knee OA who have a lower BMI, PFJ osteophytes and lower functional

self-efficacy, as each of these characteristics emerged as a predictor on more than one outcome measure. As this study was exploratory in nature and involved only a relatively small number of participants, our findings are not conclusive but hypothesis generating for further research. It is possible that more sensitive measures of structural changes in OA, such as measurement of cartilage volume on MRI, joint-space width on radiographs or the use of alternative osteophytic grading systems to the simplistic dichotomous system used in this study may reveal clearer and more consistent relationships between disease patterns of OA and outcome with glucosamine. As the present study evaluated only the symptomatic effects of glucosamine, future studies should attempt to evaluate the characteristics that are associated with a favourable treatment outcome with regard to the progression of disease.

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