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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Is glucosamine effective for osteoarthritis?

Authors: Stephanie Harrison-Muñoz**[1,2]**, Valentina Rojas-Briones**[1,2]**, Sebastián Irarrázaval**[2,3]**

Affiliation:
[1] Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[2] Proyecto Epistemonikos, Santiago, Chile
[3] Departamento de Traumatología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

E-mail: sirarraz@med.puc.cl

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Abstract

Osteoarthritis is the most prevalent chronic articular disease, in which pain is one of the main symptoms and a major determinant of functional loss. Several therapeutic options have been proposed, including glucosamine, but its actual usefulness has not yet been established. To answer this question, we searched in Epistemonikos database, which is maintained by screening multiple databases. We identified 11 systematic reviews including 35 randomized trials answering the question of interest. We extracted data, conducted a meta-analysis and generated a summary of findings table using the GRADE approach. We concluded it is not clear whether glucosamine decreases pain or improves functionality in osteoarthritis because the certainty of the evidence is very low.

Problem

Osteoarthritis is the most common chronic joint disease in the world, and is associated with progressive and chronic joint cartilage damage. During the last few years several pharmacological treatments have emerged, including glucosamine, an endogenous aminosaccharide that would slow down the proteoglycan constituents of the articular cartilage, avoiding alterations in its structure that contribute to the degenerative process. The exogenous administration of glucosamine would allow a restoration of the cartilage, which would translate into a clinical improvement. However, its actual effectiveness in osteoarthritis has not yet been clearly established.

Methods

We used Epistemonikos database, which is maintained by screening multiple databases, to identify systematic reviews and their included primary studies. With this information, we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach, and a table of other considerations for decision-making.

Key messages

- It is not clear whether glucosamine decreases pain or improves functionality in osteoarthritis because the certainty of the evidence is very low.
- Existing systematic reviews do not incorporate a substantial number of existing trials, so a new review could provide further insights.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 11 systematic reviews [1],[2],[3],[4],[5],[6],[7],[8],[9],[10],[11], including 35 randomized controlled trials, reported in 36 references [12],[13], [14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28], [29],[30],[31],[32],[33],[34],[35],[36],[37],[38],[39],[40],[41],[42],[43], [44],[45],[46],[47].
What types of patients were included	Twenty-seven trials included outpatients [15],[16],[17],[19],[20],[21],[22], [24],[25],[26],[27],[28],[29],[30],[31],[32],[33],[36],[37],[38],[39],[40], [41],[42],[43],[45],[47], four trials inpatients [12],[13],[14],[18] and in four trials this information was not described [23],[34],[44],[46]. Twenty-nine trials included patients with knee osteoarthritis [16],[17],[18], [19],[20],[21],[22],[23],[24],[25],[26],[27][28],[30],[31],[32],[33],[34], [36],[37],[38],[39],[41],[42],[43],[44],[45],[46],[47], one trial included patients with hip osteoarthritis [40], one trial included patients with osteoarthritis at more than one site [14] and in four trials this information was not described [12],[13],[15],[29].
What types of interventions were included	Twenty-nine trials used glucosamine sulfate [12],[13],[14],[15],[17],[18], [19],[20],[21],[22],[25],[26],[27],[28],[29],[31],[32],[33],[34],[36],[37], [38],[40],[41],[42],[43],[44],[45],[46], five trials glucosamine hydrochloride [23],[24],[30],[39],[47], and in one trial this information was not described [16]. Regarding dosing, twenty-eight trials used 1500 mg/day [14],[15], [17],[18],[19],[21],[22],[24],[25],[26],[27],[28],[29],[31],[32],[33],[34], [36],[37],[38],[39],[40],[41],[42],[43],[44],[47], two trials used 1500 mg/day for seven days followed by 400 mg/day for the rest of the treatment duration [12],[13], two trials used 2000 mg/day [30],[45], one trial 400 mg two times per week [20] and in two trials this information was not described [16],[23]. In thirty-one trials the route of administration was oral [14],[15],[17],[18], [19],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30],[31],[32],[33],[34], [36],[37],[38],[39],[40],[41],[42],[43],[44],[45],[46],[47], in one trial intraarticular [16], in other trial intramuscular [20], in other trial intraarticular or intramuscular followed by oral administration [12] and in other intramuscular or intravenous followed by oral administration [13]. Four trials reported that patients received adjuvant therapy in addition to glucosamine: acetaminophen [24],[45], naproxen, ibuprofen, acetaminophen or acetyl salicylic acid [29], and exercise [44]. The duration of treatment was on average 30 weeks, with a minimum of two weeks and a maximum of three years. One trial did not report this information [23]. Twenty-nine trials compared against placebo [12],[14],[15], [16],[19],[20], [21],[23],[24],[25],[26],[27],[28],[29],[30],[31],[32],[33],[36],[38],[39], [40],[41],[42],[43],[44],[45],[46],[47], three trials compared glucosamine with ibuprofen [17],[18],[22], one trial compared to piperazine/chlorbutanol for seven days followed by two weeks of placebo [13], one trial compared glucosamine sulfate against glucosamine hydrochloride [34], and one trial against Uncaria guianens (herbal supplement known as "cat's claw") [37].
What types of outcomeswere measured	The outcomes pooled by the systematic reviews identified were pain, Lequesne's index, WOMAC (Western Ontario and McMaster Universities Arthritis Index) pain subscale, WOMAC stiffness subscale, WOMAC functionality subscale, and WOMAC total, minimum joint space width, overall assessment of the disease by the patient and by the physician and drug toxicity.

Summary of findings

The effects of glucosamine are based on 21 randomized trials that, in total, included 2,691 patients. The other trials did not report any outcome of interest, or did not present the information in a way it could be incorporated in a meta-analysis. Twenty-one trials [12],[13],[14],[15],[16],[21],[24],[25],[26],[27],[28],[29],[31],[32],[33],[36],[38],[40],[41],[44],[46] measured pain (2,691 patients) and 12 trials [24],[26],[27],[28],[29],[31],[32],[36],[38],[40],[41],[44] reported functionality (2,105 patients). Adverse effects were obtained directly from one of the systematic reviews identified [5], since it was not possible to extract more information from the other reviews. The summary of findings is as follows:

- It is unclear whether glucosamine decreases pain in osteoarthritis because the certainty of the evidence is very low.
- It is unclear whether glucosamine improves functionality in osteoarthritis because the certainty of the evidence is very low.
- Glucosamine has no adverse effects or these are minimal. The certainty of the evidence is high.

Glucosamine for osteoarthritis

Patients Osteoarthritis
Intervention Glucosamine
Comparison Placebo

Outcomes	Absolut effect *	Relative effect (95% CI)	Certainty of the evidence (GRADE)
Pain (measured with different scales)	The pain scale was on average 0.46 standard deviations lower than in the group without glucosamine. SMD -0.46 (95% CI -0.69 to -0.23)	--	⨁◯◯◯[1,2,3] Very low
Functionality (measured with different scales)	The functionality scale was on average 0.13 standard deviations lower than in the group without glucosamine. SMD -0.13 (95% CI -0.33 to 0.06)	--	⨁◯◯◯[1,2,3] Very low
Adverse effects	No difference between glucosamine and placebo	RR 0.99 (0.91 to 1.07)	⨁⨁⨁⨁ High

RR= Risk ratio.
SMD = Standardized mean difference.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* Standardized mean difference is calculated when the outcome is measured using different scales, and its clinical interpretation is difficult. A rule of thumb a value of 0.2 SD represents a small, 0.5 a moderate, and 0.8 a large difference.

[1] The certainty of the evidence was downgraded for risk of bias of the primary studies assessed by the systematic reviews.
[2] The certainty of the evidence was downgraded for inconsistency, because the results for this outcome differ substantially across the different trials.
[3] The certainty of the evidence was downgraded for high risk of publication bias, as suggested by the funnel plot.

About the certainty of the evidence (GRADE)*

⨁⨁⨁⨁
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⨁⨁⨁◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⨁⨁◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⨁◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- Although the intent of this summary was to encompass all possible joints, most of the primary studies focus on knee osteoarthritis. However, in the absence of direct evidence for other articulations, it is reasonable to extrapolate the conclusions of this summary. Therefore, the evidence presented in this summary is broadly applicable to patients with osteoarthritis.

About the outcomes included in this summary

- The chosen outcomes were pain and functionality because they are the critical outcomes for decision-making on the use of glucosamine. This selection is based on the opinion of the authors of this summary, but generally agrees with the outcomes mentioned by the systematic reviews and clinical guidelines.
- No radiological outcomes were selected because they are surrogate outcomes and do not necessarily lead to clinical outcomes.

Balance between benefits and risks, and certainty of the evidence

- It is not possible to make an appropriate balance between benefits and risks because of the uncertainty about benefits.

What would patients and their doctors think about this intervention

- Faced with the evidence presented in this summary, most patients and clinicians should lean against the use of this intervention.
- However, in the absence of clearly effective therapeutic alternatives, there may be variability in clinical decisions made by individual patients. Those who favor more the possible benefit, even if it is not proven, could lean in favor of the intervention. Those who privilege more the certainty of the evidence or the costs, possibly lean against.
- There should be less variability in the decisions made by clinicians given the recommendations against the use of this intervention in the main guidelines.

Resource considerations

- It is not possible to make an appropriate balance between benefits and costs because of the uncertainty about benefits.

Differences between this summary and other sources

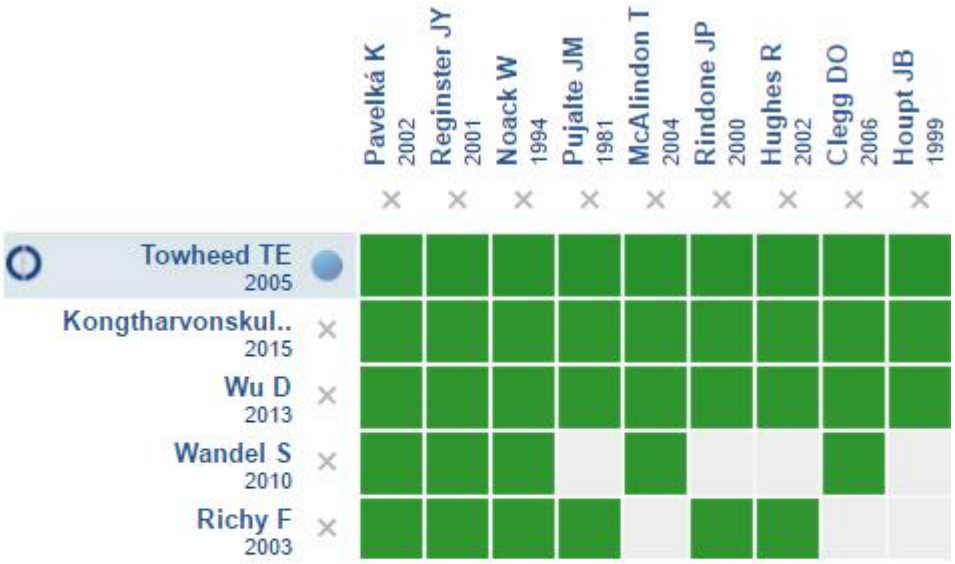
- The findings of the different systematic reviews differ from each other; five of them [1],[2],[4],[9],[11] report that it would have an effect on one of the two critical decision-making outcomes selected for this summary (pain and functionality), although some highlight there is high risk of bias. In contrast, three reviews [3],[6],[8] indicate it would have no effect on any of the aforementioned outcomes. On the other hand, two systematic reviews [7],[10] did not measure relevant clinical outcomes, only substitutes. Finally, the Cochrane review [5] indicates there would be no effects derived from the use of glucosamine in general, but suggests that a specific preparation would present better results. It is important to note that all reviews identified have important limitations, either in their completeness, methodological quality or degree of updating.
- The conclusions of this summary are consistent with the main international guidelines on osteoarthritis. The guidelines of the Osteoarthritis Research Society International (OARSI) [48] state it does not modify the disease for all patients and its usefulness for the management of symptoms is uncertain. The guideline of the American Academy of Orthopedic Surgeons (AAOS) [49] does not recommend the use of glucosamine for patients with symptomatic knee osteoarthritis.

Could this evidence change in the future?

- The probability that future research changes the conclusions of this summary is very high, due to the uncertainty of the current evidence.
- There are at least 15 ongoing studies [50],[51],[52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64], evaluating the use of glucosamine in osteoarthritis according to the International Clinical Trials Registry Platform of the World Health Organization.
- A new systematic review with high methodological quality, including all existing trials, could provide further insights into this issue.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Glucosamine for osteoarthritis

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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Author address:
[1] Escuela de Medicina
Pontificia Universidad Católica de Chile
Diagonal Paraguay 362
Oficina 310
Santiago Centro
Chile