Research Paper Review

This review is published with the permission of Research Review Service (www.researchreviewservice.com)

1. Glucosamine supplementation demonstrates a negative effect on intervertebral disc matrix in an animal model of disc degeneration.
Spine 2013; 38(12): 984–990

Jacobs L, Vo N, Coelho JP, et al.

2. Effect of glucosamine on pain-related disability in patients with chronic low back pain and degenerative lumbar osteoarthritis. A randomized controlled trial.
JAMA 2013; 304(1): 45–52

Wilkens P, Scheel IB, Grundnes O, et al.

Reviewed by Dr. Daniel Avrahami DC (Research Review Service)

ABSTRACT 1

Study Design: *Laboratory based controlled in vivo study*

Objective: *To determine the in vivo effects of oral glucosamine sulfate on intervertebral disc degeneration*

Summary of Background Data: *Although glucosamine has demonstrated beneficial effect in articular cartilage, clinical benefit is uncertain. A CDC report from 2009 reported that many patients are using glucosamine supplementation for low back pain (LBP), without significant evidence to support its use. Because disc degeneration is a major contributor of LBP, we explored the effects of glucosamine on disc matrix homeostasis in an animal model of disc degeneration.*

Methods: *Eighteen skeletally mature New Zealand White rabbits were divided into four groups: control, annular puncture, glucosamine, and annular puncture+glucosamine. Glucosamine treated rabbits received daily oral supplementation with 107mg/day (weight based equivalent to human 1500mg/day). Annular puncture surgery involved puncturing the annulus fibrosus (AF) of 3 lumbar discs with a 16G needle to induce degeneration. Serial MRIs were obtained at 0, 4, 8, 12, and 20 weeks. Discs were harvested at 20 weeks for*

determination of glycosaminoglycan(GAG) content, relative gene expression measured by RT-PCR, and histological analyses.

Results *The MRI index and NP area of injured discs of glucosamine treated animals with annular puncture was found to be lower than that of degenerated discs from rabbits not supplemented with glucosamine. Consistent with this, decreased glycosaminoglycan was demonstrated in glucosamine fed animals, as determined by both histological and GAG content. Gene expression was consistent with a detrimental effect on matrix.*

Conclusions: *These data demonstrate that the net effect on matrix in an animal model in vivo, as measured by gene expression, MRI, histology, and total proteoglycan is anti-anabolic. This raises concern over this commonly used supplement, and future research is needed to establish the clinical relevance of these findings.*

ABSTRACT 2

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

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

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

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

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

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

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

Trial Registration: *clinicaltrials.gov Identifier: NCT00404079.*

ANALYSIS

Background Information

You may not know this, but one of the most commonly used treatments for low back pain (LBP) is glucosamine. In fact, millions of people turn to glucosamine for their low back pain every year. Where do they get the idea that this could be helpful? Most of the time, from us - healthcare professionals! Many clinicians recommend patients use these supplements to help with osteoarthritic (OA) type conditions, which includes low back pain sufferers. The research literature surrounding this recommendation, however, is conflicting. There is some clinical evidence to support the use of oral supplements, such as glucosamine, for articular cartilage and intervertebral disc degeneration. In contrast, there have been many studies that showed no benefit. Since glucosamine naturally occurs in cartilage tissues it has been widely used for treating osteoarthritis, but its role in nucleus pulposus cells is largely unknown. For patients and clinicians, recommending this 'natural' supplement can seem like a no-brainer when compared to some of the alternatives, like non-steroidal anti-inflammatory drugs (NSAIDs), which can have some pretty unfavorable side effects. Make sense, right? Well, not so fast. There are some inconsistencies that exist in the literature - variability in study design, patient inclusion, and glucosamine formulation. So where does the truth lie?

Two recent, interesting studies were conducted to determine, clinically and biologically, whether glucosamine supplementation can help with low back pain, intervertebral and arthritic lumbar spine problems. The first study by Jacobs et al. aimed to determine the in vivo effects of oral glucosamine sulfate on intervertebral disc degeneration. The second study by Wilkens et al. investigated the effect of glucosamine in patients with chronic LBP and degenerative lumbar OA through disability measures (Roland Morris Disability Questionnaire [RMDQ]), pain-rating scales (at rest and during activity) and the quality-of-life measures (EuroQol-5 Dimensions [EQ-5D]).

PERTINENT RESULTS

Jacobs et al. – Effect of Glucosamine on Disc Degeneration (in vivo)

The magnetic resonance imaging index and NP (nucleus pulposus) area of injured discs of glucosamine treated animals with annular puncture was found to be lower than that of degenerated discs from rabbits not supplemented with glucosamine. Importantly, the NP area demonstrated a statistically significant effect of time at the 8, 12, and 20 week time points for annular puncture + glucosamine animals, whereas the annular puncture alone animals did not show a significant time effect until the 20-week time point. This shows that there was a more rapid decline in NP area in the glucosamine fed group. Similarly, histological analysis and content analysis demonstrated decreased glycosaminoglycan in glucosamine fed animals.

The gene expression outcome measure for glucosamine on the disc demonstrated detrimental effects. Non-injured discs of glucosamine treated rabbits had statistically significantly lower GAG content in

the NP and AF (annulus fibrosus) compared with discs of untreated rabbits and a negative effect on disc homeostasis. In the AF, the glucosamine groups demonstrated slightly increased collagen I expression but decreased collagen II expression. In the NP, the gene expression was decreased in the injured glucosamine treated group. These changes did not reach statistical significance.

Wilkens et al. – Glucosamine for LBP & Lumbar OA (RCT)

The glucosamine group had mean RMDQ scores of 9.2 at baseline and 4.8 at the one year mark. The placebo group had mean RMDQ scores of 9.7 at baseline and 5.5 at the one year mark. There was no statistically significant difference in change between groups when assessed after the 6-month intervention period and at 1 year. Interestingly, of all the patients (n = 208), 44.2% (92) guessed they received glucosamine as the study medication but of those receiving glucosamine, 52.4% (54 of 103) correctly guessed their medication and 62.9% of those receiving placebo (66 of 105) correctly guessed their medication allocation (P = .06).

CLINICAL APPLICATION & CONCLUSIONS

Osteoarthritis involves degeneration of the cartilage in joints as well as bony changes. Glucosamine is a biological building block for the molecules from which cartilage is made. Commonly used as a supplement, it is purported to slow down the degeneration that occurs in our joints. However, Jacobs et al. found that glucosamine seems to negatively affect disc matrix as observed by a decrease in the total disc GAG content, decrease in the MRI index, and NP area, worsening proteoglycan and cellularity on histological analysis, and decreased matrix gene expression. It is important to remember that these results, demonstrating the net effect on matrix metabolism, were obtained in an animal model in vivo.

In this study the researchers fed the animals for 30 days prior to administration of the annular puncture (disc degeneration provocation). Clinically, this protocol models a patient who was already taking glucosamine, maybe for other reasons, and experienced an annular injury. This means that the results from this study cannot be extrapolated to chronic degeneration, like that in osteoarthritis. However, one might reasonably think that the negative effects on matrix would potentially be more detrimental during chronic degeneration. Further to this point, glucosamine has been suggested to have anti-inflammatory effects and would be most beneficial early after an acute injury. This would suggest that the negative anabolic effects may actually be more detrimental later in the disease course, where such high levels of inflammation are not present. This study does bring up some interesting clinical concerns regarding the use of glucosamine for disc degeneration. However, to determine the clinical relevance of this study, we need some human trials to really understand the true nature of these results.

The Wilkens et al. study found there was no benefit of glucosamine compared to placebo. Basically, this indicates that you would get the same result from taking sugar pills as taking glucosamine! If you're confused and frustrated – so am I! This study had some problems regarding the study design. They included patients who had some degenerative joint issues in the back. However, 'back pain' is a very broad term. There are numerous reasons people get back pain. Asking glucosamine to solve such a global, possibly far reaching problem certainly is a tall order. Therefore, even with the results of this study, it is premature to conclude that glucosamine has no benefit for any patients with OA in the spine. There may be a subgroup of patients that would see some benefit…

If we look at the results from the Wilkens study, both groups had less back pain and less disability after treatment and at the end of the study. However, the improvement may be the result of the natural history for both groups. People feel better when they believe they are treated. Also, let's face it; patient's come see us when their condition is at its worst. This period is usually followed by a good period. This pattern is the natural development and progression of many cases or episodes of low back pain.

The inclusion criterion for Wilkens study was problematic as well. They had a large sample size with patients broadly representative of patients with chronic LBP with lumbar OA and degeneration. The etiology of LBP is incompletely understood and LBP studies are faced with a diagnostic challenge. Alternative inclusion criteria might have provided a more glucosamine receptive population. However, other studies that showed a positive effect for glucosamine did not select patients on the basis of pain-related disability. This one did. All LBP patients do not have the same pathophysiology. Understanding the pathways affected by glucosamine may allow for prediction of which patients may respond to the treatment, if any. More directed clinical trials are needed to have a greater chance of demonstrating efficacy.

One final point worth making is that glucosamine may be more effective in more severe conditions and body parts other than the lumbar spine (i.e. knee OA). The results from the Glucosamine/chondroitin Arthritis Intervention Trial suggest that glucosamine might be more effective for moderate to severe knee pain than for minimal to moderate knee pain (1). In addition, OA of the knee may contain more of the pro-inflammatory target for glucosamine than OA of the hip or low back – we can't be certain yet. Fully understanding the potential mechanism(s) of action for glucosamine is what we're missing at this point. Better understanding of these mechanisms will help us apply this type of therapy in a manner that would be most helpful.

STUDY METHODS

Jacobs et al. – Effect of Glucosamine on Disc Degeneration (in vivo)

This study used glucosamine sulfate from Wonder Labs Inc. (White House, TN) which was obtained as a crystalline powder. This lot was separately analyzed by an independent, private laboratory (BioQuant Inc., San Diego, CA) and found to have over 93% purity with no measurable heavy metal contamination. Eighteen skeletally mature New Zealand White rabbits were divided into 4 groups: control, annular puncture, glucosamine, and annular puncture + glucosamine. Rabbits were pre-fed glucosamine for 30 days. All animals underwent baseline MRIs immediately prior to annular puncture. Annular puncture was used to induce disc degeneration. The Glucosamine treated rabbits received daily oral supplementation with 107 mg/d (weight based equivalent to human 1500 mg/d). Rabbits were followed with serial MRIs at 0, 4, 8, 12, and 20 weeks. Discs were harvested at 20 weeks for determination of glycosaminoglycan content, relative gene expression measured by real time polymerase chain reaction, and histological analyses.

Wilkens et al. – Glucosamine for LBP & Lumbar OA (RCT)

This study investigated the effect of glucosamine in patients with chronic LBP and degenerative lumbar OA. This was a double-blind, randomized, placebo controlled trial conducted at Oslo University Hospital Outpatient Clinic, Oslo, Norway, with 250 patients older than 25 years of age with chronic LBP (> 6 months) and degenerative lumbar OA. Magnetic resonance imaging (MRI) scans no older than 1 year prior to inclusion consisting of at least 1 axial view (T2 weighted) and 2 sagittal views (T1

and T2 weighted) were required for inclusion. Patients had to fulfill at least 1 of the following MRI criteria: disc signal intensity changes (gray, dark, or black), reduced disc height compared with adjacent superior discs, facet joint changes (grade 1 or grade 2), modic changes (type 1, type 2 or type 3), or high-intensity zone (present or not present). The trial participants were randomized to receive a daily dose of 1500 mg of glucosamine sulfate (Glucosamine, Pharma Nord, Vejle, Denmark) or placebo, each administered as three 500-mg capsules, which could be taken one by one throughout the day or all at once over a period of 6 months. Placebo consisted mainly of cellulose. After the 6-month intervention period, the participating patients were free to choose LBP management according to their own preference. Follow-up visits occurred at 6 weeks, 3 and 6 months, and 1 year. The primary outcome was pain-related disability measured with the Roland Morris Disability Questionnaire (RMDQ). Secondary outcomes were numerical scores from pain-rating scales of patients at rest and during activity, and the quality-of-life EuroQol-5 Dimensions (EQ-5D) instrument.

STUDY STRENGTHS / WEAKNESSES

Jacobs et al. – Effect of Glucosamine on Disc Degeneration (in vivo)

After oral supplementation glucosamine was determined, through bioavailability analysis, to reach the disc tissue in the NP. Therefore, it is plausible that the effect on disc matrix observed in this study is a direct effect of glucosamine on disc cell metabolic activity. One weakness with this study revolved around the outcome measures which did not distinguish between a decrease in matrix synthesis versus an increase in matrix catabolism, and therefore the mechanism of the induced effect was unknown. Further, human studies are required to determine the clinical relevance of these findings.

Wilkens et al. – Glucosamine for LBP & Lumbar OA (RCT)

Strengths of this study include the double-blind design, high adherence rate, lack of industry involvement, 6-month and 1-year follow-up, intention- to treat analysis, and independent data monitoring. These are really strong components of the study. Contamination was reduced in the study as Glucosamine is considered a prescription drug in Norway. Successful randomization was indicated by well-balanced groups at baseline and non-significant difference (P = .06) between the groups, when testing for success of blinding, and group similarity for attrition and adverse events indicate successful blinding.

Several weaknesses were noted above. Another significant weakness of this trial had to do with the free participation in the study may have attracted a certain type of patients with specific personality traits toward this type of setting (and glucosamine) which could have affected the outcome. Further, another notable weakness that must be considered is that the patients did receive adjunctive management, which may have influenced the results from the study.

Additional References

1. Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 2006; 354(8): 795-808.