

REVIEW

Is there any scientific evidence for the use of glucosamine in the management of human osteoarthritis?

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Abstract

Glucosamine in its acetylated form is a natural constituent of some glycosaminoglycans (for example, hyaluronic acid and keratan sulfate) in the proteoglycans found in articular cartilage, intervertebral disc and synovial fluid. Glucosamine can be extracted and stabilized by chemical modification and used as a drug or a nutraceutical. It has been approved for the treatment of osteoarthritis (OA) in Europe to promote cartilage and joint health and is sold over the counter as a dietary supplement in the United States. Various formulations of glucosamine have been tested, including glucosamine sulfate and glucosamine hydrochloride. *In vitro* and *in vivo* studies have uncovered glucosamine's mechanisms of action on articular tissues (cartilage, synovial membrane and subchondral bone) and justified its efficacy by demonstrating structure-modifying and anti-inflammatory effects at high concentrations. However, results from clinical trials have raised many concerns. Pharmacokinetic studies have shown that glucosamine is easily absorbed, but the current treatment doses (for example, 1,500 mg/day) barely reach the required therapeutic concentration in plasma and tissue. The symptomatic effect size of glucosamine varies greatly depending on the formulation used and the quality of clinical trials. Importantly, the effect size reduces when evidence is accumulated chronologically and evidence for the structure-modifying effects of glucosamine are sparse. Hence, glucosamine was at first recommended by EULAR and OARS for the management of knee pain and structure improvement in OA patients, but not in the most recent NICE guidelines. Consequently, the published recommendations for the management of OA require revision. Glucosamine is generally safe and although there are concerns about potential allergic and salt-related side effects of some formulations, no major adverse events have been reported so far. This paper examines all the *in vitro* and *in vivo* evidence for the mechanism of action of glucosamine as well as reviews the results of clinical trials. The pharmacokinetics, side effects and differences observed with different formulations of glucosamine and combination therapies are also considered. Finally, the importance of study design and criteria of evaluation are highlighted as new compounds represent new interesting options for the management of OA.

Introduction

Glucosamine is an amino sugar that is essential for the biosynthesis of glycosylated proteins and lipids. It is a major constituent of extracellular matrix macromolecules such as glycosaminoglycans (GAGs), glycolipids and glycoproteins in its acetylated form. It is present in high quantities in articular cartilage, intervertebral disc and synovial fluid [1]. Glucosamine can also be extracted

from the chitosan and chitin exoskeleton of crustaceans such as shellfish and may be stabilized as a salt, glucosamine hydrochloride or glucosamine sulfate for oral administration. It has been used for many years in the treatment for osteoarthritis (OA). In Europe it is a registered drug approved for the treatment of OA (mainly for its symptomatic, slow acting effect in promoting cartilage and joint health). It has been designated an 'over the counter' dietary supplement by the US Food and Drug Administration.

Glucosamine was first thought to provide building blocks (substrates) for the biosynthesis of cartilage extracellular matrix. Subsequent investigations have found further explanations for its anti-inflammatory and anti-catabolic mechanisms of action. *In vitro* and *in vivo*

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Table 1. Recommendations for the use of glucosamine in the management of osteoarthritis

Reference	Recommendation
OARSI [2,3,7]	'Treatment with glucosamine and/or chondroitin sulphate may provide symptomatic benefit in patients with knee OA. If no response is apparent within 6 months treatment should be discontinued'
EULAR [5]	Knee OA: 'There is growing evidence to support the use of two of these agents for their symptomatic effects - namely, glucosamine sulphate (1A) and chondroitin sulphate (1A), but for the others the evidence is weak or absent'
[4]	Hip OA: 'SYSADOA (glucosamine sulphate, chondroitin sulphate, diacerhein, avocado soybean unsaponifiable, and hyaluronic acid) have a symptomatic effect and low toxicity, but effect sizes are small, suitable patients are not well defined, and clinically relevant structure modification and pharmacoeconomic aspects are not well established'
ACR [6]	'While a number of studies support the efficacy of both glucosamine and chondroitin sulfate for palliation of joint pain in patients with knee OA, the subcommittee believes that it is premature to make specific recommendations about their use at this time because of methodologic considerations, including lack of standardized case definitions and standardized outcome assessments, as well as insufficient information about study design in a number of these published reports'
NICE [81]	'The use of glucosamine or chondroitin products is not recommended for the treatment of osteoarthritis'

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; NICE, National Institute for Health and Clinical Excellence; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International.

studies have detailed different lines of evidence for how glucosamine can act on joint tissues from OA patients. In addition, many clinical trials have demonstrated various degrees of efficacy for glucosamine in OA patients. Based on the published data, the Osteoarthritis Research Society International (OARSI) [2,3] and the European League Against Rheumatism (EULAR) [4,5] have recommended the use of glucosamine sulfate for the management of knee and hip OA. In contrast, the American College of Rheumatology (ACR) [6] and the UK National Institute for Health and Clinical Excellence (NICE) have not recommended glucosamine in the management of OA (Table 1). None of the current guidelines have recommended the use of glucosamine hydrochloride, only glucosamine sulfate. Finally, it is important to point out that OARSI recommends that treatment with glucosamine sulfate is discontinued if no symptomatic response is apparent within 6 months of use. OA recommendations are outlined in Table 1. More recently, a change in evidence following a systematic cumulative update of research published through January 2009 has been reported by OARSI's treatment guidelines committee [7]. This meta-analysis reported a gradual decrease in the effect size (ES) when evidence from randomized controlled trials (RCTs) was chronologically evaluated. The study highlighted the controversy surrounding the efficacy of glucosamine in terms of both pain and structure modifications. The meta-analysis has highlighted the heterogeneity of outcomes in the different RCTs and the presence of publication bias. From a scientific perspective, the new concerns raised by the recent meta-analyses will undoubtedly stimulate a re-evaluation of the mechanistic effects of glucosamine.

The use of glucosamine in the management of OA remains controversial and its specific mechanism of action in OA pain and function modification are still unclear. The objective of this review is to address the

question raised in the title: is glucosamine still an option in the management of OA? This review summarizes the effects of glucosamine in OA based on *in vitro* and *in vivo* results as well as recent clinical trials. Special attention is given to the pharmacokinetics of glucosamine, its side effects and the differences observed with different formulations and combination therapies. Finally, based on these observations, a conclusion is drawn on the role of glucosamine in the management of OA in the context of new compounds and new combinations.

Update on *in vitro* data

The anabolic effects of glucosamine were primarily thought to be attributable to its capacity for providing building blocks for the synthesis of GAGs by chondrocytes [8-10]. Other effects have also been reported, however, such as its anti-catabolic potency, seen by its inhibition of the expression and/or activity of catabolic enzymes such as phospholipase A₂, matrix metalloproteinases or aggrecanases [11,12]. Another study confirmed the potency of glucosamine to inhibit the expression and activity of aggrecanase-2 (a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS-5)) in transiently transfected cell lines [13]. The authors suggested that the symptomatic and functional effects of glucosamine would be justified by the fact that glucosamine interferes with the matrix metalloproteinases responsible for proteoglycan degradation in OA.

Various properties were demonstrated for glucosamine in the three main tissues involved in OA, cartilage, synovial membrane and subchondral bone. The main potencies were shown in articular chondrocytes, where glucosamine was demonstrated to reverse the deleterious effects of IL-1 β [11,14,15]. In rat and human chondrocytes, the glucosamine effect was shown to occur through the inhibition of NF- κ B signaling [16,17]. The reversal of the effects of IL-1 β in human chondrocytes also inhibited

inflammatory enzymes, such as the inducible form of nitric oxide synthase and cyclooxygenase-2 [18]. This effect of glucosamine was further detailed by Imagawa and co-workers [19], who were able to demonstrate that glucosamine prevents the demethylation of specific CpG sites in the IL-1 β promoter, consequently preventing the expression of IL-1 β .

A recent pharmacoproteomic study revealed that glucosamine (10 mM) differentially regulates the pattern of expression of IL-1 β -induced proteins in human articular chondrocytes [20]. The proteins affected by glucosamine are mainly involved in the signal transduction pathways, redox and stress response, protein synthesis and protein folding. In addition, glucosamine increased the expression of the GRP78 chaperone protein. This observation supports the reported anti-inflammatory effect of glucosamine. This study also compared glucosamine to chondroitin sulfate; these compounds produced different patterns of protein modification when tested alone or in combination [20]. A synergistic effect for the modification of superoxide dismutase expression was demonstrated when cells were exposed to both compounds, implying a potent effect on oxidative stress in addition to the modulation of energy production and metabolic pathways produced by chondroitin sulfate.

The pro-anabolic effects of glucosamine were demonstrated in both human chondrocytes and synovial cells, where glucosamine was shown to induce the production of hyaluronic acid (HA) and to directly enter the GAG biosynthetic pathway (that is, for the production of HA, keratan sulfate and sulfated GAGs) [21]. The authors also proposed that the chondroprotective effect of glucosamine results from the modulation of enzymes responsible for HA synthesis.

The potential of glucosamine to induce HA production in the synovial membrane was previously suggested in a study that used synovial explants [22]. In addition, cationic glucosamine derivatives were shown to produce an anti-inflammatory effect through the inhibition of mitogen-activated protein kinase signaling pathways in lipopolysaccharide-stimulated macrophages [23].

Glucosamine sulfate was also shown to be effective in human OA osteoblasts [24]. Glucosamine increased the osteoprotegerin/receptor activator of nuclear factor kappa-B ligand (RANKL) ratio and reduced bone resorption. This effect was increased when glucosamine was used in combination with chondroitin sulfate.

It is important to point out that these studies were performed in different culture systems, with various formulations and concentrations of glucosamine. The details of the culture systems and the formulations are provided in Table 2. The concentrations used in the *in vitro* studies were 'super physiological' - in some cases up

to 2,000 times higher than the maximal concentration that can realistically be achieved in plasma (10 μ M) after oral administration of 1,500 mg of glucosamine sulfate in human subjects. Furthermore, some of these studies compared the effects of two formulations of glucosamine in order to provide evidence for the superiority of one or another [21,22,25,26]. It was proposed that the differences, if they truly existed, might contribute to the different results observed in clinical trials with various glucosamine formulations. For example, glucosamine sulfate was shown to be a stronger inhibitor of gene expression than glucosamine hydrochloride [25]. Both formulations were commercially available from a lab supplier. The same group compared glucosamine hydrochloride to N-acetylglucosamine [22] and observed no effect of N-acetylglucosamine on HA production whereas glucosamine hydrochloride appeared to modulate this parameter. The same conclusion was reached in the study by Igarashi and colleagues [21]. In contrast, another study compared the effect of native glucosamine and N-acetylglucosamine on the metabolic activity of human articular chondrocytes [26]. Both compounds exhibited different potencies on glucose transport, and GAG and HA synthesis. Indeed, N-acetylglucosamine appeared to accelerate the facilitated glucose uptake and increase both GAG and HA synthesis, suggesting that N-acetylglucosamine may be more efficient than native glucosamine.

Glucosamine has also been tested in combination with chondroitin sulfate *in vitro*. Some of the results have already been discussed above [20,24]. The effect of combinations of glucosamine and chondroitin was also reported by Chan and colleagues [27-30]. Glucosamine hydrochloride was tested in combination with chondroitin sulfate on bovine cartilage explants. The combination was shown to inhibit both inflammatory and catabolic intermediates and was slightly superior to glucosamine alone [27,28].

Finally, some authors have studied the contribution of exogenous glucosamine to the synthesis of chondroitin sulfate in human articular chondrocytes in culture [31]. They concluded that exogenous glucosamine cannot stimulate the synthesis of chondroitin sulfate. Furthermore, they showed that glucose can increase endogenous glucosamine to reach concentrations superior to those achieved after oral administration.

In conclusion, many of the *in vitro* investigations carried out so far have been performed using high concentrations of glucosamine - concentrations that are unlikely to be achieved in plasma with oral doses of the drug. Several authors have proposed that the therapeutic doses used did not allow the identification of proteoglycan synthesis as a mechanism of action of glucosamine [31,32]. Therefore, extrapolation of the *in vitro* data to the *in vivo* situation should be done with great caution.

Table 2. Principal characteristics of the *in vitro* studies testing glucosamine

Model	Concentration	Results	Reference
Glucosamine sulfate			
Human OA chondrocytes	5-500 μ M	Inhibition of PLA ₂ and collagenase in a lesser extent through PKC inhibition	[12]
Human OA chondrocytes stimulated with IL-1 β	10-1,000 mg/L	Inhibition of NF- κ B activation Inhibition of COX-2 expression and synthesis and PGE ₂ release	[17]
Human chondrocytes stimulated with IL-1 β	10 mM	Influence of the proteomic profile	[20]
Human OA cartilage explants	5 mM	Inhibition of catabolic and anabolic gene expression Superiority over glucosamine hydrochloride in the same conditions	[25]
Human OA osteoblasts	200 μ g/ml	Inhibition of pro-resorptive agents	[24]
Glucosamine hydrochloride			
Transfected cell lines	10 mM	Inhibition of ADAMTS-5 expression and activity	[13]
Human OA synovium explants	0.5-5 mM	Induction of HA production No effect of N-acetylglucosamine	[22]
D(+)-Glucosamine			
Rat chondrosarcoma cell line and bovine cartilage explants	2-16 mM	Inhibition of aggrecanase-dependent cleavage	[11]
Rat chondrocytes stimulated with IL-1 β	1-4.5 g/L	Reversion of IL-1 β deleterious effect on PG anabolism	[14]
Rat chondrocytes stimulated with IL-1 β	4.5 g/L	Inhibition of NF- κ B	[16]
Rat chondrocytes stimulated with IL-1 β	20 mM	Inhibition of inflammatory cytokines, chemokines and growth factors Inhibition of MMPs and aggrecanase-1	[15]
Human synovial cells and chondrocytes	0.1-1.0 mM	Stimulation of HA and GAG production Stimulation of HA synthase activity No effect of N-acetylglucosamine	[21]
N-acetylglucosamine			
Human chondrocytes stimulated with IL-1 β	10 mM	Inhibition of iNOS, COX-2 and IL-6 expression	[18]
Human chondrocytes	5-20 mM	Increased synthesis of GAG and HA due to acceleration of facilitated glucose uptake Superiority over native glucosamine	[26]
Human chondrocytes (normal and OA) stimulated with IL-1 β	2 mM	Prevention of the cytokine-induced demethylation of CpG site in the IL-1 β promoter resulting in decreased expression of IL-1 β	[19]

ADAMTS-5, a disintegrin and metalloproteinase with thrombospondin motifs 5; COX-2, cyclooxygenase-2; GAG, glycosaminoglycan; HA, hyaluronic acid; iNOS, inducible nitric oxide synthase; MMP, matrix metalloproteinase; OA, osteoarthritis; PG, proteoglycan; PKC, protein kinase C; PGE₂, prostaglandin E₂; PLA₂, phospholipase A₂.

Update on *in vivo* data

Several recent *in vivo* studies using different animal models have demonstrated varying potencies for glucosamine in OA. Glucosamine sulfate (200 and 400 mg/kg/day) was tested in the STR/ort mouse model of spontaneous OA [33]. Glucosamine was shown to delay the progression and severity of OA cartilage lesions. Another study reported the effect of glucosamine sulfate (250 mg/kg/day) administered to rats after anterior cruciate ligament transection (ACLT) [34]. The glucosamine treatment group showed a lower level of cartilage degradation and synovial inflammation compared to the control group. Glucosamine was also shown to modify nociception in OA rats. Mechanical allodynia and weight-bearing distribution were significantly improved by the treatment with glucosamine. In addition, the authors showed that glucosamine affected mitogen-activated protein kinase

signaling in articular chondrocytes by inhibiting p38 and JNK expression while increasing Erk1/2 expression.

The effect of glucosamine on cartilage degradation, synovial inflammation and bone resorption was recently tested in a model of collagenase-induced OA [35]. This study also compared the efficacies of glucosamine hydrochloride and glucosamine sulfate. The authors showed a better efficacy for glucosamine hydrochloride but did not provide any explanation for this difference. Indeed, glucosamine sulfate demonstrated no effect on the histological score and the formation of osteophytes whereas glucosamine hydrochloride produced a significant reduction of these parameters; glucosamine sulfate was not further evaluated. However, the results showed that glucosamine hydrochloride administered orally to OA mice (20 mg/kg/day) inhibited not only the loss of GAGs and proteoglycans in articular cartilage but also

bone resorption by the inhibition of RANKL through downregulation of bone morphogenic protein-2, transforming growth factor- β 3 and pSMAD2 and the upregulation of Dickkopf-1 protein levels in the joint. In the same study, glucosamine hydrochloride also reduced osteophyte formation and was shown to inhibit the production of the pro-inflammatory cytokine IL-6 and to upregulate the production of the anti-inflammatory cytokine IL-10 by the synovial membrane.

Glucosamine hydrochloride was also tested in the rat ACLT model of OA [36]. Glucosamine administered at a dose of 1,000 mg/kg/day produced a chondroprotective effect and reduced the serum level of the collagen degradation biomarker CTX-II. It was also tested on equine synovial inflammation induced by lipopolysaccharide injection [37]. Glucosamine hydrochloride was administered by nasogastric gavage at a dose of 20 mg/kg. This study revealed that glucosamine levels were increased in the synovium during inflammation in comparison to the healthy joint. The authors did not conclude if glucosamine produced a therapeutic effect or not. The same group has previously published results comparing the pharmacokinetics of glucosamine sulfate to glucosamine hydrochloride in horses [38]. They measured higher concentrations of glucosamine in synovial fluid after glucosamine sulfate administration than after glucosamine hydrochloride administration and concluded that glucosamine sulfate is better absorbed by the horse. Glucosamine hydrochloride was also tested in OA dogs in combination with chondroitin sulfate [39]. The combination of the two compounds reduced pain and improved weight bearing as well as reduced disease progression.

Glucosamine in the form of N-acetylglucosamine was tested in rabbits undergoing the ACLT model of OA [40]. N-acetylglucosamine was administered once a week intra-articularly at a dose of 150 mg/injection. This study suggested that glucosamine may preserve the integrity of articular cartilage but no statistical evidence was provided to support this suggestion.

Finally, glucosamine sulfate (500 mg/kg) and a combination of it with chondroitin sulfate (400 mg/kg) were compared in the rat ACLT model of OA [41]. The results showed the superiority of the combination over glucosamine alone in the prevention of biochemical and histological cartilage modifications that occur in the rat OA model.

Glucosamine has produced various effects in different *in vivo* models. It has been tested under different conditions with different formulations and dosages, tending to produce a protective effect on articular tissues. At this stage it is impossible to conclude whether one formulation is superior to another. Therefore, further studies are clearly warranted.

Clinical data

Pharmacokinetic studies

The pharmacokinetics of exogenous glucosamine has been difficult to study since glucosamine is naturally present in several biological fluids. The origin of endogenous glucosamine, if any, is unknown, although it could be speculated that endogenous glucosamine mainly results from connective tissue metabolism, since glucosamine is contained in tissues that are not consumed (for example, shellfish exoskeleton). Analytical methods have been developed in order to measure glucosamine in human plasma [42-44] and synovial fluid [45]. Most of the available data on the pharmacokinetics of glucosamine have been obtained with glucosamine sulfate; few studies have been published on the pharmacokinetics of glucosamine hydrochloride in human subjects.

The first pharmacokinetic study of glucosamine sulfate was done in 12 healthy volunteers (6 females and 6 males) after repeated oral doses [46]. Glucosamine was rapidly absorbed and available in the systemic circulation. It reached steady state after 3 hours and the maximal plasma concentration was 10 μ M after oral intake of a standard dose of 1,500 mg. The plasma concentration was shown to remain above baseline for up to 48 hours after oral administration. The elimination half-life was estimated at 15 hours, on the basis of a single oral daily dose. Pharmacokinetics were further investigated in 12 OA patients with the same regimen of administration [47]. This study revealed that glucosamine was bioavailable both in plasma and at the site of action, that is, within the joint. Glucosamine reached constant and higher levels (up to 25% higher) in the synovial fluid compared to plasma. Selective accumulation was also observed in cartilage after repeated administration of glucosamine [48]. Glucosamine was found not to bind to plasma proteins and up to 43 to 47% was associated with blood cells [49]. The authors concluded that the pharmacologically active fraction of glucosamine was the same in plasma and at the site of action.

Some information regarding the pharmacokinetics of glucosamine hydrochloride has been recently published [50]. The main purpose of this work was to study the influence of glucosamine on the pharmacokinetics of chondroitin sulfate, although this study did provide a few pharmacokinetic parameters for glucosamine hydrochloride. The authors showed that a single oral administration of 1,500 mg led to a maximal plasma concentration of 492 ± 161 ng/ml (2.28 μ M; C_{\max}) reached in 2.31 ± 1.19 h (T_{\max}). After 3 months of multiple dosing, C_{\max} was reduced to 211 ± 93.1 ng/ml (0.98 μ M) and T_{\max} was identical at 2.31 ± 1.19 h. In addition, glucosamine hydrochloride in combination with chondroitin sulfate showed a lower plasmatic level, meaning that chondroitin

sulfate inhibits glucosamine hydrochloride absorption and decreases its bioavailability [50].

Glucosamine hydrochloride and sulfate are identical from a chemical and structural point of view. The addition of salt does not justify the difference in efficacy or biological effects observed in different studies. Indeed, both glucosamine sulfate and hydrochloride dissociate in the acidic milieu of the stomach, resulting in the release of glucosamine itself [51]. It is important to bear in mind that the pharmacokinetic parameters were determined in two different systems (administration and analytical methods), which could explain the observed differences. To date, no published study has directly compared the two formulations and/or established a rigorous methodology for comparison.

Clinical efficacy

Glucosamine is classically administered orally to human subjects at a dose of 1,500 mg/day. In clinical trials involving OA patients it was shown to reduce pain and provide functional improvement [52-54] in addition to structure-modifying effects [55,56]. Several meta-analyses have summarized the efficacy of glucosamine as reported from different clinical trials [52,54,57-59]. The most recent study from Wandel and colleagues [60] analyzed the results from randomized trials with an average of at least 100 patients with hip or knee OA. The authors searched databases through to June 2010, including the most recent trials [61-64]. They retrieved a total of 10 trials (a total of 3,803 patients) that met their inclusion criteria. Their analysis reported ESs of -0.17 (-0.28 to -0.05) for joint pain and -0.16 (-0.25 to 0.00) for joint space width with glucosamine. They concluded that glucosamine produced no clinically relevant effect on pain or structure. Another recent meta-analysis concentrated on the structure-modifying effect of glucosamine [65]. The authors searched databases through 2008. They retrieved two trials meeting their criteria with glucosamine and structural modifications in OA patients. Their analysis of joint space narrowing and odds ratios revealed that glucosamine sulfate was not effective at producing structural modifications after one year of treatment, but glucosamine sulfate produced a small to moderate protective effect on minimum joint space narrowing after three years. It is important to note that this analysis was performed using just two trials.

The systematic review that is the basis for OARSI recommendations for the management of hip and knee OA was recently updated using more recent publications on glucosamine (until January 2009) [7] and highlighted many interesting points. The analysis gathered the results from 19 RCTs from a total of 20 retrieved placebo-controlled trials, including the recent ones already mentioned above. Sixteen of them used glucosamine sulfate

preparations (thirteen oral, two intra-muscular and one intra-articular) and three of them used glucosamine hydrochloride. This review revealed a decrease of ES for pain evaluated without discrimination between glucosamine preparations from 0.61 (0.28 to 0.95) in 2008 [3] to 0.46 (0.23 to 0.69) in 2010, corresponding to a moderate symptomatic efficacy [7]. The ES for pain reduction was 0.58 (0.30 to 0.87) for glucosamine sulfate, whereas it was not significant for glucosamine hydrochloride (-0.02 (-0.15 to 0.11)). However, the analysis revealed that the outcomes of trials conducted with glucosamine hydrochloride were homogenous, while those conducted with glucosamine sulfate were very heterogeneous. When considering only high quality trials, the ES for glucosamine sulfate decreased to 0.29 (0.003 to 0.57), with no publication bias but still heterogeneity outcomes of trials. The same analysis revealed a small but significant ES (0.24 (0.04 to 0.43)) for glucosamine sulfate for reduction of joint space loss in the medial compartment of knee OA patients, as reported by two sponsored RCTs [55,56], but a non-significant effect on joint space narrowing in hip OA patients after a 24-month treatment either when considering the whole study group [66] or when analyzing predefined subgroups for OA severity [64]. The same conclusion was reached by the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), with a ES of 0.15 (-0.07 to 0.38) [61]. In addition, this trial did not validate the conclusion of a study by Bruyere and colleagues [67] that glucosamine sulfate (1,500 mg/day) taken for at least 12 months reduces by half the incidence of total knee replacement, since the decision for surgical intervention is influenced by many factors. The structure-modifying effect of glucosamine on OA joints remains controversial.

Two clinical trials have been published since the publications of these meta-analyses. The results of the first one by Sawitzke and colleagues [68] were in line with the previously mentioned analysis and reported no significant difference in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain or function score with glucosamine compared to placebo. The second one by Petersen and colleagues [69] studied a different outcome: the serum level of cartilage oligomeric matrix protein, a marker of cartilage degradation. This study showed that combined with exercise, glucosamine sulfate treatment reduced the level of serum cartilage oligomeric matrix protein.

Meta-analyses have revealed the heterogeneity of outcome measures and the presence of publication bias [2,3,7]. The most recent analysis by Wandel and colleagues [60] confirms this. The analysis reported that the estimated differences between placebo and studied supplements were less pronounced in industry-independent trials compared to industry-sponsored trials. However, the retrieved trials in this analysis demonstrated less

heterogeneity. The quality of clinical trials, including study design, number of patients, outcome measures and publication bias, justified the drastic reduction of the ES observed for glucosamine over the years and trials.

Finally, the weak effect of glucosamine reported by clinical trials can be attributed to the low concentrations of glucosamine available to joint tissues [51]. Indeed, the competition that exists between glucosamine and glucose for cellular uptake favors transport of glucosamine in the intestine, liver and kidney, leaving little glucosamine available for uptake by the joint.

Side effects

Glucosamine is considered to be safe, and no serious or fatal adverse events have ever been reported from RCTs. However, several potential side effects have to be kept in mind. The first and most evident side effect of glucosamine that patients should be aware of is shellfish allergy. Indeed, glucosamine is extracted from chitin contained in shellfish and could lead to allergic reactions in certain individuals. In addition, glucosamine sulfate is administered as a salt, combined with NaCl. This formulation provides up to 30% of the daily intake of salt. This matter has to be taken into account since Na⁺ but also Cl⁻ could influence blood pressure and renal function in patients [70,71]. Finally, some human and animal studies have suggested that glucosamine can affect glucose metabolism and it has been shown to induce insulin resistance [72-75]. Despite the evidence, however, a recent comprehensive review supported by a glucosamine manufacturer has rejected these statements. The authors concluded that glucosamine had no effect on fasting blood glucose levels, glucose metabolism, or insulin sensitivity at any oral dose level in healthy subjects, individuals with diabetes, or those with impaired glucose metabolism [76]. The lack of reported adverse events during clinical trials could be attributable to the short duration of patient exposure to the treatment. Therefore, long-term treatment could be risky for diabetic and/or hypertensive patients. For these reasons, many authors recommend to monitor blood glucose concentration and blood pressure in these patients [73-75,77]. Clearly, further studies are warranted to determine the longer term effects of glucosamine on insulin sensitivity in human subjects.

Conclusion

Different formulations of glucosamine tested in various *in vitro* or *in vivo* systems have exhibited many potential mechanisms of action on articular structures. Furthermore, two of the major published guidelines recommended glucosamine sulfate in the treatment of OA pain while another integrating more recent data did not consider glucosamine sulfate. At this time, glucosamine hydrochloride cannot be recommended based on the

available clinical data. However, there are no clear indications that the effects of the two formulations can be distinguished from each other in terms of biological activity, posology or pharmacokinetics. Recent meta-analyses have reminded us of the importance of the quality of the clinical trials and this matter is more and more frequently addressed in the literature [51]. The evaluation tools and the design of clinical trials should be standardized and there are many ongoing efforts in this area [78].

Finally, it is important to note that the majority of the published clinical trials with glucosamine reported a significant ratio of subjects who failed to respond to treatment. Therefore, the question of the benefit of glucosamine treatment remains largely unanswered. One may wonder about the clinical relevance of this treatment and whether to use it with regards to the cost/benefit ratio. On the one hand, compared to non-pharmacological modalities such as exercise, weight loss or education, glucosamine is not effective with regards to pain and function, but the question of its cost compared to nonpharmacological modalities should be explored. On the other hand, glucosamine sulfate shows an ES superior to (or at least equal to) the commonly used analgesic or nonsteroidal anti-inflammatory drugs, but has no rare or adverse effects.

Therefore, based on the fact that glucosamine has low and rare adverse effects, it represents a viable option for the management of OA (as a symptomatic slow acting drug) but its administration should be discontinued if no significant effect is reported by the patient. New tools, such as novel biomarkers, are required to discriminate responders and non-responders. The use of glucosamine associated with the monitoring of response using an appropriate biomarker could improve the efficiency and the cost/benefit ratio of the treatment. Finally, we should consider the use of glucosamine as a combination therapy with other drugs or other nutraceuticals, such as omega-3 fatty acid or manganese ascorbate [79,80]. This would open up a new horizon in this field but the combinations would need to be rigorously assessed.

Abbreviations

ACLT, anterior cruciate ligament transection; ES, effect size; EULAR, European League Against Osteoarthritis; GAG, glycosaminoglycan; HA, hyaluronic acid; IL, interleukin; NF, nuclear factor; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; RANKL, receptor activator of nuclear factor kappa-B ligand; RCT, randomized controlled trial.

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Competing interests

YH has received consulting fees and educational grants from companies developing nutraceuticals, food supplements or drugs for the treatment of osteoarthritis (Nestlé, Tilman SA, Bioiberica, Pierre fabre, Merck). YH is the

founder of Artialis, a spin-off company of the University of Liège specialized in the development and commercialization of in vitro diagnostic kits. MM and MA have no competing interests.

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