Glucosamine and osteoarthritis

Alexander R Shikhman
Scripps Clinic MS113, Division of Rheumatology, 10666 North Torey Pines Road, La Jolla, California 92037, USA
Tel.: +1 858 554 8562; Fax: +1 858 554 6763; ashikhman@scrippsclinic.com

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Osteoarthritis (OA) is the most common form of arthritis and is often associated with significant disability [1–3]. The impact of OA is expected to grow as the population increases and ages over the coming decades. The etiology of OA is multifactorial. OA-affected joints are characterized by progressive degeneration of the articular cartilage, osteophytes, subchondral sclerosis and alterations of the synovial membrane and joint capsule [4]. OA is a heterogeneous condition with differences in specific joint sites; these include apparent etiologies, as well as specific clinical, pathological or radiological features [4,5]. Typical clinical symptoms are pain and stiffness, particularly after prolonged activity [5,6]. Pathological processes in OA eventually result in joint deformities and significant functional impairment [4–6].

None of the therapies currently available are capable of delaying disease progression in OA [7]. Most treatment protocols are focused on pain and stiffness relief, and on the maintenance and improvement of functional status [7–9]. Treatment strategies for OA utilize both nonpharmacological and pharmacological modalities [7–9]. Nonpharmacological therapies include weight reduction, physiotherapy and orthotics. Pharmacological agents in OA are limited to [7–9]:

- Nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX)-2 inhibitor(s)
- Simple analgesics (e.g., acetaminophen)
- Intra-articular therapy with corticosteroids and viscosupplementation devices
- Topical analgesics (e.g., capsaicin and NSAIDs)
- Over-the-counter supplements (e.g., glucosamine [GlcN] salts and chondroitin sulfate)

GlcN is commonly used by OA patients as a nutraceutical in the USA and as a pharmaceutical in Europe. However, the efficacy of oral GlcN, with regard to both symptom and disease modification in patients with osteoarthritis, remains controversial [10]. This review analyzes the biological activities of GlcN in vivo and in vitro and summarizes published data on clinical applications of this aminosugar in osteoarthritis.

**Biological activities of glucosamine in vitro**

GlcN expresses certain biological activities in vitro that may potentially contribute to its activity in vivo. These activities include:

- Interference with glucose transport and metabolism
- Modification of glycosaminoglycan synthesis
- Immunomodulation
- Inhibition of catabolic and proinflammatory responses
- Interference with chondrocyte survival

**Glucosamine & glucose metabolism**

Articular cartilage is an avascular tissue that receives its nutrients and oxygen by diffusion from blood vessels in the underlying bone and synovial fluid [11]. On a cellular basis, the consumption of oxygen by cartilage is only 2–5% of that of the liver or kidney. However, the amounts of lactate formed are comparable with those tissues [11], indicating that the energy generation in cartilage depends strongly on glucose supply [12]. Increasing concentrations of glucose suppress oxygen consumption (the Crabtree effect or catabolic repression), a phenomenon that has also been observed in articular chondrocytes [13]. Glucose is the main precursor for uridine-5'-phosphate (UDP) hexosamines.
and UDP-uronic acids, which are utilized by chondrocytes in glycosaminoglycan synthesis [14,15]. Therefore, changes in glucose uptake and metabolism affect quantitative and qualitative composition of cartilage matrix proteoglycans. Glucose concentration also modifies chondrocyte responses to certain growth factors, such as insulin-like growth factor (IGF)-1 [16], suggesting that glucose plays a key role in chondrocyte activation.

Transmembranous transport of glucose is facilitated by a group of highly specialized glucose-transporter proteins (GLUTs) [17]. Glucose transport in human articular chondrocytes is facilitated by at least five distinct GLUTs: cytokine-inducible GLUT-1 and -6 (formerly GLUT-9) and constitutively expressed GLUT-3, -8 and -10 [18,19]. Facilitated glucose transport in chondrocytes is insulin independent and regulated by proinflammatory cytokines and growth factors [18,19].

It has been well documented that in insulin-sensitive cells, such as myocytes and adipocytes, GlcN suppresses facilitated glucose transport and induces insulin resistance via the inhibition of the plasma membrane translocation of the insulin-dependent glucose transporter GLUT-4 [20]. Moreover, parenteral administration of GlcN also resulted in insulin resistance and suppressed GLUT-4 translocation to the cell membrane in skeletal muscle cells. Control infusions of galactosamine and mannosamine had no effect on glucose uptake and GLUT-4 membrane translocation [21]. The exact molecular pathways sustaining GlcN-induced insulin resistance are not completely understood. Among the current hypotheses explaining this phenomenon are: activation of protein kinase C and increased flux of glucose through the hexosamine pathway [22], depletion of ATP stores [23] and aberrant activation of Akt kinase [24].

GlcN inhibits glucose transport in unstimulated, cytokine- and growth-factor-stimulated human articular chondrocytes [25]. GlcN-regulated inhibition of glucose transport in chondrocytes is mediated via the suppression of expression and plasma membrane incorporation of inducible GLUT-1 and -6 proteins [25]. Owing to dependence of chondrocyte homeostasis on appropriate glucose supply, GlcN-induced changes in glucose transport can have profound effects on various chondrocyte functions.

Similar to glucose, imported GlcN is phosphorylated to GlcN-6-phosphate (P) by hexokinase in mammalian cells [26,27]. Accumulated GlcN-6-P inhibits hexokinase [27], which serves as a sensor and regulator of glucose transport [28–30].

The destiny of intracellular GlcN-6-P depends on the activity of GlcN-6-P deaminase/isomerase, the enzyme converting GlcN-6-P to fructose-6-P [31] that can be further utilized by glycolytic enzymes [32]. The expression and activity of GlcN-6-P deaminase in cartilage tissue and chondrocytes, as well as its ability to utilize supraphysiologic concentrations of intracellular GlcN-6-P, are unknown.

In contrast with glucose-6-P, GlcN-6-P demonstrates distinct activities toward glucose-utilizing metabolic pathways, including the hexosamine pathway, glycolysis and the pentose-monophosphate shunt.

GlcN-6-P enters the hexosamine pathway efficiently by bypassing glutamine-fructose 6-P amidotransferase, a gate-keeping enzyme of the hexosamine pathway [33], and via a series of nonrate-limiting enzymatic reactions is converted to UDP-N-acetylhexosamine [24,35] that can be utilized for glycosaminoglycan synthesis [36] and protein O-glycosylation [37]. However, GlcN-induced inhibition of glucose transport and GlcN-6-P allosteric inhibition of glutamine-fructose 6-P amidotransferase [38] reduces glucose flux through the hexosamine pathway. Therefore, the global effect of GlcN on glycosaminoglycan synthesis depends on the balance between these two processes.

GlcN and GlcN-6-P have a biphasic effect on glycolysis [39]. At low concentrations, they stimulate glycolysis and ATP production [39]. This may be explained, in part, by the conversion of GlcN-6-P to fructose-6-P, a substrate for glycolysis [31,32]. At a high concentration, GlcN and GlcN-6-P reduce lactate production and ATP accumulation [40] by inhibiting two enzymes of the glycolytic pathway: glyceraldehydes-3-P-dehydrogenase and lactate dehydrogenase [39].

The pentose-P shunt represents a vital metabolic pathway regulating energy generation and inactivation of reactive oxygen radicals [40,41]. It has been demonstrated that GlcN-6-P inhibits activity of glucose-6-P dehydrogenase (a key enzyme of the pentose-monophosphate shunt) in a dose-dependent fashion and suppresses nicotinamide adenine dinucleotide phosphate (NADP)⁺ accumulation [42].

In summary, GlcN interferes with glucose transport and glucose metabolism in mammalian cells. Most of the measurable effects of
Glucosamine & cartilage

Glycosaminoglycan synthesis

Cartilage glycosaminoglycans are the key structural components of the extracellular cartilage matrix. Glycosaminoglycan loss is a feature of the aged and degenerated cartilage [43]. Prevention of glycosaminoglycan loss and acceleration of their synthesis are important components of chondroprotective strategies.

Different experimental approaches have been used to determine the effect of GlcN on extracellular cartilage matrix synthesis. GlcN can be imported by cells and incorporated into newly synthesized glycosaminoglycans [44]. UDP-N-acetylgalactosamine, the end products of the hexosamine pathway, are the precursors for glycosaminoglycan synthesis. Sweeney and colleagues demonstrated that, in Swarm rat chondrosarcoma cells, only one in 375 UDP-N-acetylgalactosamine is derived from the exogenous GlcN in the presence of glucose [45]. By contrast, Noyszewski and colleagues demonstrated that GlcN is preferentially incorporated into galactosamine moieties of chondroitin sulfate at levels that were 300% higher than the equivalent amount of glucose [46]. Bassler and colleagues reported that GlcN sulfate, at low and medium micromolar concentrations, accelerated the production of proteoglycans in cultured human articular chondrocytes without affecting the length of glycosaminoglycan chains and the rate of DNA and collagen II synthesis [47]. Mroz and Silbert showed that, at submillimolar concentrations, GlcN has no effect on sulphated glycosaminoglycan synthesis, whereas high concentrations of GlcN inhibit this process [48,49]. Similar findings were published by de Malaté and colleagues [50].

These variations among the experimental results, probably reflect the fact that GlcN plays a dual role in cell physiology: it efficiently enters the hexosamine pathway by bypassing glutamine-fructose 6-P amidotransferase, a gate-keeping enzyme of the hexosamine pathway; and enters the pool of UDP-N-acetylgalactosamines [33–35]. However, it also inhibits facilitated glucose transport [25] and thus, can potentially decrease glucose flux through the hexosamine pathway. Therefore, the global effect of GlcN on glycosaminoglycan synthesis depends on the balance between these two pathways.

Glucosamine & chondrocyte activation by catabolic stimuli

It is well documented that proinflammatory cytokines, including interleukin (IL)-1β and tumor necrosis factor (TNF)-α, play a pathophysiological role in the development and progression of OA by initiating a sequence of catabolic events leading to the degradation of extracellular cartilage matrix and cartilage degeneration [51]. Treatment of articular chondrocytes with proinflammatory cytokines stimulates the production of collagen II degrading metalloproteinases [52], activates the matrix-degrading enzymes aggrecanase [53] and hexosaminidase [54], induces nitric oxide [55], COX-2 [56] and IL-6 [56] synthesis and suppresses the synthesis of sulfated glycosaminoglycans [57]. The increased production of IL-1β has been described in aged and OA cartilage [58]. Therefore, therapeutic agents possessing anticatabolic properties may potentially benefit chondroprotection.

Most of the existing data indicate that, at low millimolar concentrations, GlcN expresses anticatabolic and anti-inflammatory activities.

Pretreatment of equine cartilage explants with GlcN suppressed IL-1 and lipopolysaccharide-induced extracellular matrix degradation, as measured by a reduction of sulphated glycosaminoglycan release [59]. GlcN also inhibited IL-1α and lipopolysaccharide-induced nitric oxide and metalloproteinase release [59]. Previously, the author demonstrated that GlcN inhibited activation of human articular chondrocytes by IL-1β, as measured by nitric oxide production and expression of inducible nitric oxide synthase, COX-2 and IL-6 [60]. The inhibitory effect of GlcN on IL-1 responses did not depend on the suppression of IL-1-inducible mitogen-activated protein kinase (MAPK) activation or nuclear factor (NF)-κB nuclear translocation [60]. GlcN and several other hexosamines inhibited IL-1α and retinoic-acid-induced degradation of the extracellular matrix in rat chondrosarcoma cells and bovine cartilage explants via the inhibition of aggrecanase activity [61,62]. GlcN also inhibited the expression of another IL-1-inducible catabolic enzyme, stromelysin-1 [63]. Activation of chondrocytes...
with IL-1 results in the suppression of sulphated glycosaminoglycan synthesis, which is mediated, in part, via the downregulation of glucuronosyltransferase-1 expression [63]. This inhibitory effect of IL-1 was prevented by GlcN [63].

At low millimolar concentrations, GlcN exhibited anticatabolic activity and delayed aggregan degradation in bovine cartilage explants exposed to retinoic acid [64]. Byron and colleagues showed that, in cultured equine chondrocytes, GlcN inhibited mRNA and protein expression of several metalloproteinases, including matrix metalloproteinase (MMP)-1, -3 and -13, but had no effect on MMP activation [65]. Similarly, Dodge and Jimenez demonstrated the inhibitory effect of GlcN on MMP-3 production in human articular chondrocytes [66].

The exact molecular mechanisms mediating anticatabolic activity of GlcN are still poorly understood. The proposed mechanisms include: upregulation of IL-1β Type II decoy receptor [67], activation of protein kinase C [68], suppression of NF-κB nuclear translocation [67] and the inhibition of glycosylphosphatidylinositol-linked protein synthesis [69].

Thus, most of the published data indicate that GlcN expresses anticatabolic activity in cultured chondrocytes. The exact molecular mechanisms of GlcN-mediated anticatabolic activities remain to be defined. A major limitation of in vitro studies on GlcN is that its effects are observed predominantly at lower millimolar concentrations, which exceed the range of therapeutic concentrations obtained with oral GlcN by a factor of $10^2-10^3$ [70-72].

Effect of glucosamine on immune & inflammatory responses

Inflammatory changes associated with OA include synovitis [73,74] and joint effusions [75]. They represent important mechanism of joint pain in OA patients [75] and can contribute to the progression of cartilage degeneration [76]. Morphologically, OA synovium is characterized by synovial hyperplasia [74] and increased cellular infiltrates consisting of macrophages and CD4+ helper T lymphocytes [77].

GlcN-mediated immunomodulation can also be part of its anti-arthritic mechanisms. Ma and colleagues demonstrated that GlcN inhibited the induction and effector function of alloreactive cytotoxic murine T cells, suppressed activation of T lymphoblasts and dendritic cells, as well as allogeneic mixed leukocyte reactivity in a dose-dependent manner [78]. Furthermore, GlcN administration prolonged allogeneic cardiac allograft survival in vivo [78]. Similarly, Forchhammer and colleagues reported that, at low millimolar concentrations, GlcN suppressed unprimed T-cell responses by interfering with antigen-presenting cell functions and by a direct inhibitory effect on T-cell proliferation [79]. In addition, GlcN inhibited the secretion of cytokines in antigen-stimulated unprimed T cells and primed T-helper (Th)-2-polarized cells [79]. Yagita and colleagues reported that GlcN inhibited human natural killer cell activity [80]. By contrast, Matheron and colleagues described natural killer activity in normal human peripheral blood mononuclear cells as significantly elevated in the presence of $10^{-4}$ and $5 \times 10^{-4} \text{M} \text{GlcN}$ [81].

GlcN is known also to modify neutrophil functions. GlcN suppresses superoxide anion generation and inhibits phagocytosis, the release of lysozyme and neutrophil chemotaxis [82]. In addition, GlcN reduces formyl methionyl leucylphenylalanine-induced upregulation of CD11b, polymerization of actin and phosphorylation of p38 MAPK [82]. Therefore, the anti-inflammatory property of GlcN can potentially contribute to the reduction of synovitis and symptom modification in arthritis. However, dose responses are still the main obstacles precluding the direct extrapolation of the in vitro data into in vivo models and clinical practice.

Glcosamine & apoptosis

Programmed cell death, or apoptosis, of chondrocytes is observed in cartilage impact injuries and may be part of the mechanisms leading to cartilage degeneration [83-85]. There are no data available indicating that GlcN protects chondrocytes from proapoptotic stimuli. On the contrary, supratherapeutic GlcN concentrations can induce cell death.

The ability of GlcN to induce cell death in malignant cells has been recognized for several decades. The cytostatic or cytotoxic effects of GlcN were reported for various tumor cell lines including L1210 leukemic cells [86], rat C6 glioma [87], mastocytoma P-815 [88], human colon carcinoma [89], hepatoma M-c29 [90], myeloma protein in ascites (MOPC)-21 [91] and human malignant epithelial cells [92]. In most of the reports, the cytotoxic effect of GlcN was observed at low millimolar concentrations. Until recently, the cytotoxic effect of GlcN was considered as an almost exclusive attribute of transformed or malignant cells. However, in
Nakamura and collaborators reported that GlcN induces apoptosis in cultured, non-transformed retinal neurons [93]. Later, de Mattei and colleagues showed that exposure of bovine cartilage explants to high concentrations of GlcN (above 20 mM) results in chondrocyte death [50].

The principal execution pathway (apoptosis vs oncosis) mediating GlcN-induced cell death is still undefined. Possible mechanisms of GlcN-induced cytotoxicity include:

- Surplus accumulation of UDP-N-acetylhexosamines [92]
- Interference with protein glycosylation [86]
- Inhibition of acetate incorporation into non-esterified sterols and lipids [94,95]
- Depletion of ATP stores [88]
- Inhibition of thymidine kinase [96]
- Inhibition of N-myristoyl transferase [97]

The author's data demonstrate that GlcN reproducibly induces cell death of human articular chondrocytes in vitro at concentrations exceeding 15 mM. GlcN-induced chondrocyte cell death represents a caspase-independent process. GlcN is also capable of inducing chondrocyte death upon its intra-articular administration [98].

Based on the dose-response curves, GlcN-induced chondrocyte death should not be a matter of concern in patients taking oral GlcN. However, it can represent a problem upon intra-articular administration of highly concentrated GlcN preparations.

Biological activities of glucosamine in animals with experimental arthritis

To determine whether GlcN possesses anti-arthritis activities in vivo, the author analyzed published articles regarding the in vivo effects of GlcN on inflammatory responses, cartilage morphology and cartilage biochemistry.

The effect of GlcN on synovitis was studied predominantly in small, experimental animals utilizing models of inflammatory arthropathies. The efficacy of GlcN in the therapy of synovitis associated with OA is a poorly studied topic.

Orally administered GlcN sulfate expressed anti-arthritis activity in rats with kaolin-induced arthritis and adjuvant arthritis [99]. The anti-inflammatory/anti-arthritis activity of GlcN was 50-300-fold lower than that of indomethacin [99]. GlcN expressed modest anti-inflammatory activity against edema induced by carrageenan, dextran and formalin. GlcN also protected rats against carrageenan-induced pleuritis. Furthermore, GlcN protected animals against peritonitis provoked in the rat by formalin and in the mouse by acetic acid [100]. GlcN did not show antinoceptive properties against pain provoked by intraperitoneal phenylquinone in mice. GlcN did not inhibit COX or proteolytic enzymes in the inflamed paw, but it was able to inhibit in vitro superoxide generation and lysosomal enzymes of the liver. The anti-inflammatory potency of GlcN was lower than that of acetylsalicylic acid, and much lower than that of indomethacin [100].

Oral administration of GlcN at supratherapeutic concentrations suppressed synovitis and cartilage degeneration induced by adjuvant arthritis in mice [101]. Similarly, oral administration of a combination of GlcN, chondroitin sulfate and manganese ascorbate in rats with collagen-induced arthritis significantly reduced arthritis severity [102].

Recently, the author demonstrated that intra-muscular administration of GlcN in rabbits with experimental knee OA secondary to anterior cruciate ligament transection does not improve synovitis scores [103].

GlcN efficacy in experimental OA has mainly been studied in rabbits. Daily dietary supplementation with GlcN chloride at supratherapeutic concentrations did not significantly retard cartilage degeneration in rabbits with knee OA [104]. By contrast, daily administration of GlcN at therapeutic concentrations in rabbits with experimental knee OA induced by anterior cruciate ligament transection did not affect cartilage surface integrity (fibrillations and erosions) but improved focal safranin O scores in the lateral tibial plateaus. However, this was not confirmed by the biochemical analysis of sulfated glucosaminoglycan content [105]. Oegema and colleagues reported that oral administration of GlcN at supratherapeutic doses in rabbits with chymopapain-induced arthritis restored sulfated glycosaminoglycan content in the degenerated cartilage [106]. Oral GlcN did not affect sulfated glycosaminoglycan/proteoglycan content of the normal temporomandibular articular disc in rabbits [107]. Intramuscular administration of GlcN in rabbits with anterior cruciate ligament transection did not significantly affect OA scores in the treated animals, as compared with controls [103].

Kobayashi and colleagues analyzed the effect of GlcN (supratherapeutic doses) combined with chondroitin sulfate on cartilage degeneration in...
rabbits after partial medial meniscectomy. The authors did not demonstrate any benefits of such a combination on cartilage scores, including MMP-1 scores, in the treated animals. However, addition of fursulthiamine, a vitamin B1 derivative, to the GlcN/chondroitin combination produced a measurable chondroprotective effect [108].

The analyzed published data did not reveal any benefits of GlcN administration on cartilage surface integrity (prevention of cartilage fibrillation and erosion) and on collagen synthesis and degradation.

In summary, most of the published data indicate that GlcN might express anti-inflammatory activity in animal models of inflammatory arthropathies. By contrast, the data on chondroprotective activity of GlcN in animals with experimental OA are still nonconclusive. Among the factors affecting the heterogeneity of these results are various routes and doses of the administered GlcN, as well as the absence of uniform criteria for the evaluation of GlcN chondroprotective activity in animals.

Glucosamine pharmacokinetics & toxicity

The pharmacokinetics of GlcN have been reviewed in detail in several publications [70, 109]. Therefore, in this review, the author would like to emphasize several key points.

The absorption of orally administered GlcN is nearly 90% [70]. After absorption, GlcN is incorporated into plasma proteins during first-pass metabolism, resulting in 26% bioavailability [110]. A recent attempt to analyze the bioavailability of escalating doses of GlcN produced inconclusive results due to imperfections in the study design (absence of intravenous GlcN dosing, which is considered as 100% bioavailable) [111].

The baseline concentration of the endogenous serum GlcN in humans varies from 10 to 200 ng/ml [111]. After oral ingestion, the peak of serum GlcN occurs between 90 to 180 min, with a concentration range of 0.3–2.0 μg/ml [112].

Although GlcN exists mainly as an oral preparation, several topical formulations containing GlcN are also used in the therapy of OA [113]. Analysis of the transdermal permeability of GlcN in rats demonstrated a permeation rate of 13.27 μg/cm²/h at 5% concentration, which was considerably higher than the one predicted for hydrophilic substances [114].

Clinically relevant dosing of GlcN in humans and large animals (horses) results in serum and synovial fluid concentrations that are at least 500-fold lower than those reported to modify chondrocyte anabolic and catabolic activities in tissue- and cell-culture experiments [112, 115].

Despite the fact that the currently recommended daily dose of oral GlcN is 1500 mg, formal analysis of the dose-response curves in OA symptom modification has never been performed in dedicated clinical trials.

Oral administration of GlcN at supratherapeutic doses (5000–15,000 mg/kg body weight) is well tolerated without documented toxicity. The lethal dose for 50% survival (LD₅₀) for GlcN for rats, mice and rabbits exceeds 5000 mg/kg, with a median value of more than 8000 mg/kg [109]. In small animals, GlcN has an excellent safety profile upon chronic and subchronic administration [116]. GlcN does not possess mutagenic activity [109]. Analysis of the clinical data demonstrates that GlcN does not possess toxicity upon chronic administration in humans [109].

It is known that administration of GlcN at supratherapeutic concentrations in animals induces insulin resistance [21, 117]. Intravenous infusion of high-dose GlcN in humans also reproduced certain features of diabetes [118]. However, oral administration of GlcN in patients with OA has not been associated with an increased risk of glucose intolerance or diabetes [119, 120].

Although available data indicate that chronic oral administration of GlcN at currently used doses (1500– 3000 mg per day) does not possess a risk of major adverse events, systematic analysis of GlcN-associated cardiovascular or renal adverse events has never been performed. Furthermore, drug interactions involving GlcN is another practically unknown topic that requires further research.

Glucosamine use in patients with OA

GlcN was introduced to the therapy of OA almost 40 years ago [121, 122]. The initial rationale for their use in OA was based on the notion that supplementation of patients with glycosaminoglycan precursors, including GlcN and its derivatives (N-acetylglucosamine, N-acetylglactosamine, etc.) will accelerate glycosaminoglycan synthesis in articular cartilage and thus restore tissue integrity in the affected joints [121, 122]. It has been well recognized that GlcN plays an important role in cartilage...
homeostasis. Excessive urinary loss of this aminosugar, which takes place in patients with aspartylglucosaminuria, leads to the development of chronic arthritis [123]. The wide use of GlcN in OA was also stimulated by the description of its anticatabolic and anti-inflammatory properties in vitro. However, the main discrepancy between these in vitro experiments and the use of GlcN in humans is based on the fact that this aminosugar produces measurable biological effects in vitro when used at millimolar concentrations that exceed concentrations achievable in the joint upon oral administration by more than 100–1000-times [70–72]. This raises doubts that the effects observed in vitro represent a plausible mechanism of action in vivo.

Analysis of published reports indicates that most of the published clinical trials on GlcN are focused on symptom modification in patients with knee OA.

In 1980, Pujalte and colleagues reported that patients taking oral GlcN experienced a substantial reduction in joint pain as compared with those taking placebo [124]. Similar results were obtained in a multicenter clinical trial where 1200 patients with knee OA were treated with oral GlcN [125].

Intra-articular and intramuscular administration of GlcN was reported to reduce pain and increase the range of knee motion [126,127]. Using a different clinical protocol, D'Ambrosio and colleagues reported that, in patients with knee OA, parenteral (intravenous or intramuscular) administration of GlcN followed by oral intake diminished joint pain to a greater extent than placebo [128]. Oral GlcN produced analgesic effects similar to the NSAID drug ibuprofen [129,130]. By contrast with those studies, Houpt and colleagues reported that, in the best designed studies, GlcN taken orally does not benefit knee pain and function [10]. Pooled results from the analyzed studies showed a trend towards superiority of GlcN sulfate versus GlcN chloride in the treatment of pain and functional impairment resulting from symptomatic OA [10]. However, no dedicated clinical trials have ever formally compared the efficacy of GlcN sulfate versus GlcN chloride in OA symptom modification. Hypothetically, one can propose that increased consumption of sulfate can potentially produce a mild cartilage-specific anabolic effect via interference with sulfation of the extracellular matrix glycosaminoglycans.

Recently, the National Institutes for Health summarized the data from a large multicenter, placebo-controlled clinical trial comparing the symptom-modifying activity of GlcN chloride (alone and combined with chondroitin sulfate) with celecoxib and chondroitin sulfate in patients with symptomatic OA of the knee. Monotherapy with GlcN chloride did not reveal any superiority over placebo with regard to pain reduction in patients with both mild and moderate-to-severe knee pain. Combination therapy of GlcN chloride with chondroitin sulfate was found to be statistically superior to placebo only in patients with moderate-to-severe knee pain [136].

Several studies have attempted to analyze the effect of oral GlcN on cartilage metabolism utilizing surrogate biomarkers. Cibere and colleagues did not find statistically significant differences in urine and serum collagen type II fragment levels between patients with knee OA treated with GlcN sulfate versus placebo [137]. Similarly, Christgau and coworkers failed to demonstrate an effect of oral GlcN on urine collagen type II C telopeptide [138]. However,
patients with a high cartilage turnover were found to be more responsive to GlcN-mediated symptom modifications [138].

The efficacy of GlcN in patients with OA affecting joints other than the knee is practically unknown. Several published studies describe the results of the use of GlcN in combination with chondroitin sulfate to treat discogenic lower back [139] and OA affecting the temporomandibular joint [140]; however, the impact of GlcN when used in combination cannot be assessed accurately.

In summary, the existing dilemma of GlcN is based on the fact that its popularity among patients with OA is not strongly supported by the clinical evidence of its disease- or symptom-modifying activity.

Conclusions

Despite the currently existing controversies surrounding GlcN, this aminosugar remains a popular and widely consumed remedy to treat symptoms of OA. In academic settings, glucosamine represents a useful probe to study the molecular mechanisms of chondrocyte homeostasis and activation. Although GlcN expresses anti-inflammatory properties in vivo, its chondroprotective activity in animals with experimental OA is minimal, if any. The main obstacles preventing the universal acceptance of GlcN among physicians practicing evidence-based medicine are the lack of reproducible, unbiased and brand-independent data on the clinical utility of GlcN in OA and a marked gap between biologically efficient GlcN concentrations in vitro and therapeutically achievable GlcN concentrations in vivo.

Future perspective

The story of GlcN, obviously, is not over yet. Debates around GlcN re-emphasized the issue on the absence of current or foreseeable pharmaceutical agents possessing disease-modifying activity in OA and thus, are capable of preventing, or even restoring, cartilage integrity impaired by the disease. The lessons learnt from GlcN demonstrate that a simple monosaccharide can express a broad concentration-dependent range of biological effects in vitro that can be potentially exploited for the sake of chondroprotective interventions. Therefore, in the near future we can expect an emergence of GlcN derivatives or analogs combining chondroprotective and anti-inflammatory activities and having therapeutically attractive dose-response profiles both in vitro and in vivo. The discrepancy between the biologically efficient and therapeutically achievable GlcN concentrations will also be conquered by the introduction of GlcN analogs or derivatives suitable for transdermal or intra-articular applications.

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**Executive summary**

**Introduction**

- Osteoarthritis (OA) is the most common form of arthritis characterized by the progressive degeneration of articular cartilage, osteophytes, subchondral sclerosis and alterations of the synovial membrane and joint capsule. None of the currently available therapies are capable of delaying disease progression in OA.

- The aminosugar glucosamine (GlcN) is commonly used by OA patients as a nutriceutical in the USA and as a pharmaceutical in Europe.

**Biological activities of glucosamine in vitro**

- GlcN expresses certain biological activities in vitro that may potentially contribute to its activity in vivo. These activities include: 1) interference with glucose transport and metabolism; 2) modification of glycosaminoglycan synthesis; 3) immunomodulation; 4) inhibition of catabolic and proinflammatory responses; and 5) interference with chondrocyte survival.

**Biological activities of glucosamine in animals with experimental arthritis**

- GlcN possesses certain anti-inflammatory activities in animal models of inflammatory arthropathies. In contrast, the data on chondroprotective activity of GlcN in animals with experimental OA are still inconclusive.

**Glucosamine use in patients with OA**

- The clinical data on symptom- and disease-modifying activities of GlcN in OA are still controversial.

**Conclusions**

- The main discrepancy between in vitro GlcN activities and the use of this aminosugar in humans is based on the fact that GlcN produces measurable biological effects in vitro when used at millimolar concentrations. This exceeds the concentrations achievable in biological fluids upon oral administration by more than 100–1000-times.
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Glucosamine and osteoarthritis – REVIEW


• Review of GlcN pharmacokinetics and toxicity.


Affiliation
• Alexander R Shikhman, M.D., PhD
Scripps Clinic M 5113, Division of Rheumatology, 10666 North Torrey Pines Road, La Jolla, California 92037, USA
Tel.: +1 858 554 8562;
Fax: +1 858 554 8562;
asikhman@scrippscin.com

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