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Review

The effects of oral glucosamine on joint health: is a change in research approach needed?

J. A. Block†‡*, T. R. Oegema‡§, J. D. Sandy‡§ and A. Plaas†‡
† *Department of Internal Medicine (Rheumatology), Rush University Medical Center, Chicago IL, USA*
‡ *Department of Biochemistry, Rush University Medical Center, Chicago IL, USA*
§ *Department of Orthopedic Surgery, Rush University Medical Center, Chicago IL, USA*

Summary

Objective: Oral glucosamine (GlcN) has been widely studied for its potential therapeutic benefits in alleviating the pain and disability of osteoarthritis (OA). Its popularity has grown despite ongoing controversy regarding its effectiveness vs placebo in clinical trials, and lack of information regarding possible mechanisms of action. Here, we review the state of knowledge concerning the biology of GlcN as it relates to OA, and discuss a framework for future research directions.

Methods: An editorial "narrative" review of peer-reviewed publications is organized into four topics (1) Chemistry and pharmacokinetics of GlcN salts (2) Biological effects of GlcN salts *in vitro* (3) Therapeutic effects of GlcN salts in animal models of OA and (4) GlcN salts in the treatment of clinical OA.

Results: Data reporting potent pleiotropic activities of GlcN in *in vitro* cell and explant cultures are discussed in the context of the established pharmacokinetic data in humans and animals. The available clinical trial data are discussed to place the patient in the context of controlled research on disease management.

Conclusions: Future research to determine therapeutic mechanisms of GlcN salt preparations will require use of standardized and clinically relevant *in vitro* assay systems and *in vivo* animal models for testing, as well as development of new outcome measures for inflammation and pain pathways in human OA.

Key words: Glucosamine, Osteoarthritis, Cartilage, Hexosamine metabolism, Inflammation, Therapeutics.

Abbreviations: GlcN, glucosamine ($C_6H_{13}NO_5$); OA, Osteoarthritis; GAG, glycosaminoglycan; GLUT, glucose transporter.

Introduction and overview

Oral glucosamine (GlcN) is widely used both in Europe and in the US in an attempt to palliate the pain and disability of osteoarthritis (OA), and is a component of a large number of dietary supplements in the US. It has also garnered great interest in the fitness and athletics communities because of claims that it has cartilage building and lubricant properties for the joints[1]. Its popularity has grown despite ongoing controversy regarding its effectiveness (vs placebo), safety, and possible mechanisms of action. While GlcN is highly bioactive when added to cell cultures at supra-physiologic concentrations, we confine our discussion here to its putative effects on joint disease *in vivo*, specifically on pain, mobility and structural protection.

The publication in 1996 of "The Arthritis Cure" by Jason Theodosakis, M.D. stimulated interest by the American public in oral GlcN as an effective therapeutic for OA. Theodosakis' claims for therapeutic efficacy were based largely on conversations with patients suffering from chronic OA pain. The same author published an updated version in 2004 entitled "The Arthritis Cure: The Medical Miracle That Can Halt, Reverse, and May Even Cure Osteoarthritis".[2] These books, along with widespread anecdotal reports of pain relief achieved with oral GlcN as well as the absence of clearly safe and effective therapies that retard OA progression, have resulted in the GlcN market for OA and other joint conditions (alone or in combination with other components such as chondroitin sulfate) developing into a multi-billion dollar industry in the US; a parallel industry has developed in Europe, where GlcN is available as a prescription drug.

As a result of its popularity and its potential therapeutic efficacy, GlcN has been studied intensively, and there is a great deal of information concerning its cellular mechanism of action, animal and human pharmacokinetics and clinical efficacy. Most *in vitro* studies of GlcN activity on joint tissue have been performed in the 50–5000 μM range, although some studies have been done at as low as 1 μM (see Table I) To serve as a comparison, in diabetes research the effects of 2 mM GlcN on the flux of glucose-derived intermediates through the hexosamine biosynthetic pathway (HBP) have been extensively evaluated. GlcN-dependent alterations in the activity of O-glycosylated intracellular signaling components, including increased O-N-acetyl-glucosamination of factors such as IRS, GS, PDX-1, eNOS and Sp1, have also been described[3].

*Address correspondence and reprint requests to: Joel A. Block, Rush Medical College, Rush University Medical Center, 1725 W. Harrison St., Suite 1017, Chicago, IL 60612, USA, Tel: 1-312-942-8268, Fax: 1-312-563-2267; E-mail: jblock@rush.edu
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Table I
In vitro *studies of GlcN effects on Cartilage and Chondrocytes*

Pathways assayed	Tissue or cell source	Culture condition*	Compound [Concentration range]	Reference
Aggrecan, Collagen, ECM synthesis	Murine, canine, porcine, bovine, equine & human chondrocytes Equine synovial fibroblasts Human MSC	Monolayer cultures, alginate bead cultures, ±IL-1β	GlcN.HCl [1 μM–25,000 μM] GlcN.SO4 [50 μM–5000 μM]	27, 28, 40†, 41–49, 73
Protease production	Equine and human chondrocytes Equine and human synoviocytes	Monolayer cultures + catabolic stimulators (IL-1β or LPS)	GlcN.HCl [1 μM–6000 μM] GlcN.SO4 [1000 μM–2500 μM]	40†, 47†, 50, 51
Inflammatory mediator gene expression & production	Canine, equine, human chondrocytes Rat IVD cells Equine & human synoviocytes	Monolayer cultures, alginate or agarose bead cultures, ±IL-1β	GlcN.HCl [1 μM–25,000 μM] GlcN.SO4 [50 μM–10,000 μM]	27, 47†, 48–55
Signal transduction	Equine, human &ATDC5 chondrocytes; human synovial fibroblasts; bovine chondrocytes	Monolayers ± IL-1β	GlcN.HCl [60 μM–6000 μM] GlcN.SO4 [50 μM–60 μM]	27, 51–53, 56, 73
Glucose transporters & Ion channels	Bovine chondrocytes	Monolayers + IL-1β	GlcN.HCl [1000 μM–2500 μM]	4, 6
Aggrecan degradation ADAMTS proteinase gene expression	Explants of bovine, equine and human OA cartilage	+Catabolic stimulators (IL-1β, LPS, retinoic acid & FN fragments)	GlcN.HCl [400 μM–5000 μM] GlcN.SO4 [300 μM–7500 μM]	24–26, 42, 43, 57–72
MMP/TIMP gene and protein expression	Explants of bovine, equine and human OA cartilage	+Catabolic stimulators (IL-1β, LPS, FN fragments)	GlcN.HCl [30 μM–5000 μM] GlcN.SO4 [60 μM–5000 μM]	59, 61–64, 67–69
Inflammatory mediator gene expression and production	Explants of bovine, equine and human OA cartilage	+Catabolic stimulators (IL-1β & LPS)	GlcN.HCl [60 μM–5000 μM] GlcN.SO4 [30 μM–5000 μM]	43, 62, 63, 65–70
ECM production	Explants of bovine, equine, porcine and human OA cartilages	+Catabolic stimulators (IL-1β, LPS, retinoic acid & FN fragments)	GlcN.HCl [30 μM–5000 μM] GlcN.SO4 [45 μM–5000 μM]	24, 25, 44, 58, 59, 63–69

*Note that for most studies Dulbecco's modified Eagle medium (DMEM) containing 25,000 μM glucose is used as culture medium
†References 40 and 47 found an effect of GlcN at physiologically relevant concentrations. All other studies used test concentrations >30 μM

However, pharmacokinetic studies in humans (Table II) have shown that the Cmax after recommended GlcN dosing (1500 mg per day) is approximately 10 μM; this suggests that the high concentrations that appear to be active *in vitro* (Table I) are not physiologically relevant to the action of the drug in the post-hepatic metabolism *in vivo*. Since O-glycosylation of signaling factors also occurs only at supra-physiologic concentrations[3], this mechanism does not appear to be relevant to the proposed actions of oral GlcN on joint tissues either. Some groups have recently observed effects of GlcN at *in vitro* concentrations in the 1–60 μM range[40,47]; if confirmed by independent laboratories, these studies might provide insight into clinically relevant actions of this compound on cell metabolism.

The sodium-independent facilitative glucose transporter[4–6] provides the mechanism for both glucose and GlcN uptake into cells. As the Km (extracellular concentration required for effective uptake) for both glucose and GlcN for the functional chondrocyte transporter is about 350 μM,[6] and the *in vitro* studies listed in Table I have almost exclusively been performed in culture medium containing 25,000 μM of competing glucose, only a very small percentage (perhaps 1–2%) of the GlcN added to such cell and explant cultures is likely to enter the cells. Indeed, in studies on this aspect of incorporation using exogenous GlcN concentrations of 50 μM (in the presence of 5500 μM glucose), only about 5% of the exogenous GlcN entered intracellular pathways that led to its activation to a high energy uridine diphosphate (UDP)-derivatized intermediate for subsequent usage by glycosyltransferases[7–9]. Therefore given our present understanding of functional uptake mechanisms in chondrocytes, the clinically relevant studies *in vitro*, i.e.,

Table II
GlcN pharmacokinetics: human studies

Formulation	Single dose (mg/kg/day)	No of subjects enrolled	Route	Days of dosing	C_{max}	Serum/Plasma assay	Reference
GlcN.HCl	7	40	Oral	21	3–4 μM	HPLC	81
GlcN.SO4	20	20	Oral	1	12 μM	LC/MS/MS	82
GlcN.SO4	20	12	Oral	1–3	9 μM	LC/MS/MS	83
GlcN.SO4	20	12	Oral	14	7 μM	LC/MS/MS	77
GlcN.SO4	10	22	Oral	1	2 μM	LC/MS/MS	84
GlcN.SO4	20	12	Oral	1	10 μM	LC/MS/MS	84
GlcN.SO4	20	18	Oral	1	11 μM	Amperometic	8

those which report an effect with GlcN concentrations at less than 50 μM, will need to be evaluated in light of the prevailing glucose concentration and the activity of the glucose transporter mediating cellular uptake of GlcN.

Further, when considering the situation *in vivo* it is highly likely that the intestinal lining, liver or kidney will consume a substantially higher percentage of the orally administered monosaccharide than joint tissues. This follows from the fact that each of these tissues utilizes the GLUT-2 transporter which has a Km of about 17,000 μM for glucose and 800 μM for GlcN[10]. In light of these considerations, this review seeks to evaluate objectively the current knowledge of potential intracellular mechanisms of GlcN action, focusing on those that might affect the joint following clinically relevant dosing and a therapeutically relevant C_{max} In addition, we review the clinical data on GlcN to assess the need for a re-evaluation of research efforts in this area.

Chemistry of GlcN.HCl, GlcN.sulfate salt and GlcN-3-sulfate ester

An important and often confusing aspect of GlcN usage has been the structure of the various GlcN compounds marketed for oral consumption. For example, claims have been made both by suppliers and by medical authorities that "GlcN.sulfate" is superior to "GlcN.hydrochloride". However, the only organic component in both formulations is the amino-sugar GlcN, ($C_6H_{13}NO_5$), and in this regard the formulations are chemically and structurally identical, differing only in the nature of the salt included to neutralize the proton on the amino-group of the GlcN. Whereas in GlcN.HCl, it is the chloride salt (composition, $[GlcNH^{3+}].Cl^-$), for GlcN.sulfate it is a mixture of the sulfate and the chloride salts (composition, $[GlcNH^{3+}]_2.2Na^+.SO_4^{2-}.2Cl^-$) (US Patent No. 4,642,340). When GlcN.HCl enters the human stomach (normally at pH 2.5 due to a high normal content of HCl) it dissociates completely to GlcN (the amino-sugar) and HCl (hydrochloric acid); similarly, GlcN.sulfate dissociates to the amino-sugar, HCl (hydrochloric acid), Na_2SO_4 (sodium sulfate) and H_2SO_4 (sulfuric acid). In other words, for each formulation, the only organic ingredient upon oral consumption is GlcN itself. The salts and acids generated, however, are different. On the basis that GlcN is considered to be the active ingredient in both formulations, there is no rationale available in the scholarly literature that might explain superiority of one over the other. Some[9,11,12] attempts have been made to explain the apparent superiority of GlcN. sulfate over GlcN.HCl by suggesting that the sulfate anion is limiting in the circulation[13] and therefore may provide an oral "boost" to chondroitin sulfate synthesis[14–16]. This argument also appears flawed[18] because the Km for the sulfate transporters in chondrocytes[19] has been measured at about 16 mM, a concentration that is about 50-times the serum sulfate concentration of 0.3 mM[12]. This means that ingestion of 1.5 g of GlcN.sulfate would need to increase the serum sulfate concentration about 50-fold to have any effect on sulfate supply, a change which appears to be impossible. In contrast, GlcN-3-sulfate, an ester in which the sulfate group is covalently bound to the hydroxyl group on carbon-3 of the hexosamine, is explicitly not present in the GlcN sulfate sold for joint health and should not be considered as an oral supplement. It is therefore critically important to clearly define the chemical structure of compounds used both *in vivo* and *in vitro* in all future research planning.

The pharmacokinetics of oral GlcN salts

We have selected for review only pharmacokinetic data from oral dosing with clinically-approved GlcN preparations. Search strategies included a PubMed review using the following search terms: (GlcN.HCl, GlcN.sulfate, OA, therapeutic, human, horse, pharmacokinetics). Eight studies of humans (Table II) and three equine studies (Table III) were identified. The horse studies are in general agreement that the C_{max} (at 2 h) is about 10 μM. In one horse study the C_{max} of the sulfate and chloride salts of GlcN were directly compared and found to be essentially identical. In the human studies (see Table II for formulation, dose and route, number of individuals studied, days of dosing before evaluating the C_{max}, C_{max} observed and the GlcN assay used), the C_{max} was determined to be between 1 and 4 h after ingestion in all cases. Importantly, in the six human studies with GlcN, sulfate salt the mean C_{max} values were consistent with the result in the one study that employed the hydrochloride salt [81]. Four of the human studies (a total of 62 subjects) were performed in independent laboratories under essentially identical conditions (a single oral dose of GlcN sulfate given to normal volunteers at 20 mg/kg, which translates to a single 1500 mg dose of GlcN in a 75 kg individual). The C_{max} results (mostly determined by mass spectroscopy) of these four studies were remarkably similar at 12,9,10 and 11 μM. Significantly, one group studied OA patients instead of normal and in this case the mean C_{max} was 7 μM. As the literature on C_{max} in humans is remarkably consistent, at about 10 μM, it seems reasonable that no further research is necessary in this area. Indeed any future use of animal models (Table III) without a confirmed C_{max} of ~10 μM seems unlikely to yield useful information about potential GlcN effects in humans.

Table III
GlcN pharmacokinetics: animal studies

Formulation	Single dose mg/kg/day	Animal	Route	Days of dosing	C_{max}	Serum/Plasma assay	Reference
GlcN.HCl	350	Rat	i.v., i.p. or oral	1	105 ± 89 μM	HPLC	74
GlcN.HCl	1600	Guinea Pig	Oral	–	1400 μM	–	75
Combination of GlcN.HCl, Chondroitin Sulfate and MnAscorbate	375	Rabbit	Oral	–	5170 μM	–	76
GlcN.HCl	100	Rabbit	Oral	–	<45 μM	–	22
Combination of GlcN.HCl, Chondroitin Sulfate	214	Dog	i.v/p.o	–	42 μM	–	17
GlcN.HCl	20	Horse	i.v. or n.g	1	50 μM or 1 μM	LC/MS/MS	78
GlcN.SO4	20	Horse	i.v. or n.g	1	50 μM or 1 μM	LC/MS/MS	78
GlcN.HCl	20	Horse	i.v. or n.g.	1	300 μM or 1 μM	FACE	79
GlcN.HCl	125	Horse	Oral	1	60 μM	HPLC	80

Biological effects of GlcN salts on cells and tissue explants *in vitro*

A collection of 29 published articles in this area is shown in Table I, but may not be exhaustive. The table provides the concentration range of GlcN salt tested. For reasons cited in preceding sections, concerning potential clinical relevance, we confine our discussion to those *in vitro* studies which have described effects at concentrations close to the physiologically relevant C_{max} of $\sim$10 μM. In the first of these studies[40], human OA chondrocytes were incubated with GlcN sulfate at concentrations ranging from 0.2 to 200 μM. Under those conditions, messenger RNA (mRNA) and protein levels of aggrecan core protein were increased with a concomitant decrease in the production and enzymatic activity of matrix metalloproteinase (MMP)-3. Significant effects were detected at 10 μM and above. In the second, using equine chondrocytes and synovial cells, GlcN.HCl at about 1 μM, was found to decrease interleukin (IL)-1 stimulated production of PGEs in both cell types[47]. Since similar effects on inhibition of enzymes of the prostaglandin synthase pathway (essential fatty acid conversion to membrane-intercalated arachidonic acid and cyclooxygenase (COX)-1/2 conversion of arachidonic acid to prostaglandins D, E and F), were seen with higher concentrations of GlcN salts (Table 1, Refs 29, 45, 50, 57, 64, 65, 67, 72), a focus of future research could be on mechanisms by which extracellular GlcN salts might interfere with this pathway. For example, extracellular GlcN salts might interfere with the receptors for E series of prostaglandins (EP receptors) required for prostaglandin uptake and the attendant pro-inflammatory effects[29]. Conversely, extracellular GlcN salts might directly regulate synthesis or translocation of Glycosylphosphatidylinositol (GPI)-anchored proteins on the cell surface; this is a particularly interesting possibility since GPI-anchored heparan sulfate-substituted proteins on the cell surface have been shown to directly activate PGE2[29], or promote arachidonic acid release by Secretory phospholipase A2 (sPLA2s)[30]. Additional studies (Table I), albeit at supra-physiologic concentrations, showed changes in gene expression or secretion of pro-inflammatory factors such as inducible nitric oxide synthase (iNOS), endothelial nitric oxide synthase (eNOS), COX-2, or prostaglandin E (PGE). These effects include suppression of u-plasminogen activator (u-PA) and MMP2/9, inhibition of NO and sulfated glycosaminoglycan (GAG) release, inhibition of gene expression of eNOS, iNOS, COX-2 and secretion of PGE, or inhibition of nuclear factor kappa B (NFkB) activity. In related studies, others have observed in chondrocyte pellet cultures, a GlcN salt-mediated inhibition of IL-1-induced PGE-2 synthase and mPGEs, blockade of the inhibitory effects of methyl prednisolone, reduced PLA2 activity and stimulated PG synthesis.

In vivo studies of GlcN salts in animal models of OA

There is a substantial literature focused on the effects of GlcN in animal models, including the combination of GlcN and chondroitin sulfate. This includes a number of studies which employed doses that markedly exceeded those used in humans, studies with a perceived conflict of interest, and studies of the *in vivo* effects of GlcN on non-articular diseases. In general, the C_{max} for GlcN in these animal studies was not determined making it difficult to evaluate therapeutic relevance for human OA.

Relevant animal models include lapine, murine and canine studies. Using an anterior cruciate ligament deficient model of acute OA in the rabbit and daily GlcN.HCl dosing for 8 weeks, starting 3 weeks after surgery, Tiraloche, *et al.* failed to detect any significant effect for most of their outcomes[20]. However, the investigators noted that there was mild protection of the articular cartilage from surface fibrillation and loss of Saffranin O staining in the lateral tibial plateau, as well as a reduction in biochemically measured sulfated GAG loss from the femoral condyles. While the lack of agreement between the site-specific effects revealed by histology vs biochemical sulfated GAG analysis was not resolved, this paper highlighted the importance of examining site-specificity in the joint and such findings are clearly relevant to human clinical evaluation. The paper also emphasizes the need for more quantifiable measures of effects at the biological level. Interestingly, a continuation of this study reported that oral GlcN may partially inhibit the high bone turnover induced by ligament transection[21], again highlighting the importance of evaluating multiple tissues in the joint rather than restricting attention to the cartilage. The authors[21] acknowledged that the major limitation of the study in extrapolating to human disease is the rapidity of onset in the model; nonetheless, the results remain relevant to possible mechanistic effects of oral GlcN on joint health. Using a different model, chymopapain-induced joint damage in the rabbit, it has been reported that oral GlcN resulted in increased cartilage GAG content in both damaged and control knees[22]. Although this model of cartilage damage may not be relevant to human OA, it suggests that oral GlcN can have a significant effect on cellular biosynthetic activity under conditions of rapid exogenously-mediated proteolytic GAG depletion from cartilage. Similar results were reported in a murine model, in which oral GlcN administered at 100 mg/kg following intra-articular injection of papain into murine knee joints significantly improved cartilage proteoglycan content at 2 weeks. In addition, the peak concentration of serum pro-inflammatory cytokines induced by papain injection occurred earlier and decreased sooner in the GlcN.HCl supplemented group. This trend was also seen in expression of these same factors by the liver. Moreover, in this experiment GlcN did not alter the percentage of mesenteric lymph node lymphocyte populations but accelerated their activation. Hence, oral GlcN appears to alter the physiology of the liver and mesenteric lymph nodes, which in turn, could indirectly alter the biology of damaged joints[23].

GlcN salts and treatment of clinical OA

Reports suggesting that GlcN may be useful clinically for the treatment of OA have been available since the 1960's and controlled clinical trials of oral, parenteral, and topical preparations abound, yet claims of GlcN's efficacy as a pain palliative and as a structure modifying agent for OA remain highly controversial. The US National Institutes of Health had intended to settle these issues with the Glucosamine/Chondroitin Intervention Trial (GAIT) study[31], which was a well-powered non-industry financed randomized double-blind controlled trial comparing GlcN to chondroitin sulfate to a combination of both, and included both placebo and positive control (celecoxib) arms. Although the primary outcomes of the trial were unambiguously null, some subgroups appeared to have significant positive effects. In addition, various editorialists have argued that the GlcN preparation that was tested by the GAIT

investigators (GlcN.HCl) was inadequate, and that positive results might have been obtained if a different preparation (GlcN.sulfate) had been employed in the trial[32,33] (see discussion of the chemistry of these formulations above). Several well-performed meta-analyses have been performed in the last decade, and two recent yet contradictory publications are representative[34,35]. Interestingly, they agree that preparations of GlcN crystallized as the hydrochloride salt are ineffective, but disagree over the therapeutic benefit of GlcN preparations crystallized as the sulfate salt. The Cochrane Collaboration's update of its systematic review of GlcN in OA concluded that whereas GlcN.HCl appears to be ineffective, studies that focused on the Rottapharm corporation's preparation of GlcN.sulfate suggest that this preparation of GlcN is significantly more effective than placebo for treating pain and function in OA[35]. These results are in contrast to those of Vlad *et al.*[34] who also considered the different GlcN preparations separately; they reported that whereas there is sufficient evidence that the GlcN.HCl preparation lacks efficacy for pain relief, the heterogeneity of trials assessing GlcN.sulfate prevents a clear conclusion regarding efficacy, though the heterogeneity appeared to be most prominent in industry-sponsored trials of GlcN.sulfate [34]. Interestingly, all published trials that were not industry sponsored have been negative, including a recent evaluation of GlcN sulfate for use in hip OA[36]. This uncertainty regarding therapeutic efficacy has been perpetuated by the controlled studies published after completion of these meta-analyses; hence, an industry-sponsored study reported that GlcN sulfate delayed OA progression to arthroplasty[37] whereas the non-industry sponsored study of hip OA failed to detect any symptomatic or structural benefits[36].

It is not our purpose to provide a definitive ruling regarding whether GlcN truly has a role in OA therapy; rather, our intention is to clarify what is known and to distinguish those areas that we believe warrant further research from others for which additional public research expenditures would be unlikely to substantively affect either our understanding or the societal use of GlcN. In that light, the following issues should be considered:

GlcN SALT FORMULATION FOR CLINICAL USE

There appears to be consensus that GlcN.HCl lacks efficacy for the palliation of pain or function in OA[34,35]. The toxicity profile appears benign, however, and the preparation appears to be safe for oral consumption. As discussed in a previous paragraph, the term "GlcN sulfate" is ambiguous, and may refer to a variety of chemical substances. It is therefore essential to be clear what is under consideration when discussing the results of clinical trials. The sulfate ester of GlcN (GlcN-3S ester), while retaining a variety of biological activities, is not a natural oral supplement and is not generally consumed as a therapeutic or adjunctive agent in clinical settings, nor have there been any randomized clinical trials of its effect in humans. In contrast, the substance commonly referred to as "GlcN sulfate" is the sulfate salt of GlcN, and as noted previously, this GlcN is pharmacologically identical to the GlcN prepared as the hydrochloride salt. Moreover, there is good experimental evidence that the sulfate salt by itself is biologically inactive *in vivo* regarding articular structures. Hence, although the possibility of clinical advantages conferred by the GlcN sulfate salt over the GlcN hydrochloride salt remains, there is at present no biological or known rational justification to explain such a putative benefit; as such, the burden of proof must rest on those who argue for such an advantage either to identify a reasonable mechanism of action or to demonstrate an unambiguous empirical advantage. It is useful to bear in mind that (1) the apparent advantages of GlcN.sulfate vs GlcN HCl rest entirely on the results of trials sponsored by the manufacturer of that proprietary preparation whereas all independent studies have been negative, (2) there appears to be publication bias in this field[38], and (3) the more recent publications tend to be less positive than the older trials[35], which may possibly be related to the recent requirement by most journals that clinical trials be publicly registered prior to their initiation. Therefore, we conclude that whereas the sulfate salt of GlcN appears in meta-analyses to offer possible efficacy for OA therapy, there is insufficient mechanistic rationale or independent empirical evidence at present to consider it to be substantively different than the hydrochloride salt of GlcN.

INTERPRETATION OF CLINICAL TRIAL DATA

Skepticism is warranted in the interpretation of meta-analyses that survey issues for which incomplete information is available. Underlying the meta-analytic method is the assumption that aggregating information from multiple studies should strengthen the power to discern actual effects. However, where the available data differ substantially from the total data collected, such as in cases of significant publication bias, meta-analyses may falsely elevate an apparent effect that might have disappeared altogether if all of the evidence were able to be considered; in extreme cases where only positive results are published, the apparent (though not necessarily real) clinical benefit would be greatly magnified by meta-analysis. We therefore counsel caution in interpreting meta-analyses that assess therapeutic agents that have not been clearly independently evaluated, or for which clear publication bias exists.

Research perspective: GlcN salts and OA management

There remains controversy concerning the rational role, if any, of GlcN in OA management. Nonetheless, analyses of public behavioral patterns suggest that consumption of oral supplements perceived to be beneficial does not change in response to evidence of lack of efficacy, whereas consumption clearly declines in response to evidence of significant toxicity. Indeed, for GlcN, publication of the GAIT data[33] garnered a great deal of publicity concerning the failure to detect clinical efficacy, however US sales remained constant in the months afterwards without any noticeable decline[39]. Therefore, in light of the apparent safety of oral GlcN preparations, as long as they are manufactured using Good Manufacturing Practice, it is likely that most consumers find the presence or absence of clinical evidence demonstrating efficacy to be irrelevant. This suggests that additional trials to elucidate groups for which GlcN might be efficacious will have little impact on public attitudes or behavior, and substantial outlays of scarce public research dollars for these purposes will not likely affect the public's approach to OA.

GlcN salts have been shown to be potent modulators of the hexosamine biosynthetic pathway and downstream O-glycosylation reactions in *in vitro* systems. However, these effects are only achieved with extracellular concentrations in the mM range, which are 100–1000 fold higher than extracellular concentrations achieved *in vivo* in joint fluid and tissues. Therefore, future research aimed at elucidating

mechanisms of action of GlcN salts for translational purposes need to be based on use of (1) standardized *in vitro* cell and tissue culture systems, (2) well characterized animal models of OA pathology, (3) therapeutically relevant preparations and concentrations of GlcN salts and (4) standardized outcome measures that include the inflammatory and pain pathways relevant to human OA.

Conflict of interest

Authors have no conflicts of interest.

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