Review

Glucosamine effects in humans: a review of effects on glucose metabolism, side effects, safety considerations and efficacy

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Abstract

Glucosamine is widely used to relieve symptoms from osteoarthritis. Its safety and effects on glucose metabolism are critically evaluated in this review. The LD_{50} of oral glucosamine in animals is $\sim$8000 mg/kg with no adverse effects at 2700 mg/kg for 12 months. Because altered glucose metabolism can be associated with parenteral administration of large doses of glucosamine in animals and with high concentrations in in vitro studies, we critically evaluated the clinical importance of these effects. Oral administration of large doses of glucosamine in animals has no documented effects on glucose metabolism. In vitro studies demonstrating effects of glucosamine on glucose metabolism have used concentrations that are 100–200 times higher than tissue levels expected with oral glucosamine administration in humans. We reviewed clinical trial data for 3063 human subjects. Fasting plasma glucose values decreased slightly for subjects after oral glucosamine for $\sim$66 weeks. There were no adverse effects of oral glucosamine administration on blood, urine or fecal parameters. Side effects were significantly less common with glucosamine than placebo or non-steroidal anti-inflammatory drugs (NSAID). In contrast to NSAID, no serious or fatal side effects have been reported for glucosamine. Our critical evaluation indicates that glucosamine is safe under current conditions of use and does not affect glucose metabolism.
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1. Introduction

Glucosamine, 2-amino-2-deoxy-ᴅ-glucose, is an amino monosaccharide that is an essential component of mucopolysaccharides and chitin. Glycosaminoglycans (mucopolysaccharides) are large complexes of negatively-charged carbohydrate chains that are incorporated into mucous secretions, connective tissue, skin, tendons, ligaments and cartilage. Glucosamine and its acetylated derivative, *N*-acetylglucosamine, are readily synthesized in the body from glucose. Because of its high concentration in joint tissues, the hypothesis that glucosamine supplements would provide symptomatic relief for osteoarthritis was developed more than 30 years ago (D'Ambrosio et al., 1981). Many clinical trials have tested this hypothesis (Institute of Medicine, 2004) and glucosamine supplements are widely used to relieve arthritic complaints (Houpt et al., 1999).

To meet the demand for glucosamine nutritional supplements, three forms of glucosamine are commonly available: glucosamine hydrochloride, glucosamine sulfate, and *N*-acetyl-glucosamine. These glucosamine compounds are generally derived from chitin, a biopolymer present in the exoskeleton of marine invertebrate animals. The glucosamine derived from chitin in the cell walls of many fungi appears to be chemically identical to that found in marine invertebrates (Institute of Medicine, 2004).

This report is a critical evaluation of the available information on the safety of glucosamine in animals and humans and its effects on glucose metabolism. The effects of glucosamine intake on blood, urine, and fecal parameters, blood pressure and pulse rate and reported side effects are summarized. NSAID are widely prescribed and purchased over-the-counter for osteoarthritic complaints but have significant side effects and are associated with >16,000 deaths annually in the US (Wolfe et al., 1999). The efficacy and safety of glucosamine for arthritic complaints will be compared to other oral preparations.

2. Biological effects

2.1. Absorption, distribution, metabolism and excretion (ADME)

Setnikar et al. (1986) administered uniformly labeled [^{14}C] glucosamine-HCl diluted with unlabeled glucosamine sulfate by intravenous and oral routes of administration to 8 male and 8 female Beagle dogs for 144 h. Samples of plasma, feces, urine, CO_2 and all organs were analyzed. Immediately after intravenous administration of radiolabeled glucosamine, 10% of the labeled glucosamine was found as free glucosamine in plasma; this was quickly cleared by the liver and kidney and excreted in urine. The remaining 90% of radioactivity in plasma was bound to or incorporated into plasma proteins. Plasma activity quickly increased reaching a peak at 8 h. During this phase, radioactivity diffused rapidly into the liver and kidney and subsequently was found in skeletal tissues and articular cartilage. After oral administration of radiolabeled glucosamine to dogs, 87% was absorbed. In the dog, there were no gender differences for any parameters.

Setnikar et al. (1984) also administered uniformly labeled [^{14}C] glucosamine-HCl diluted with unlabeled glucosamine sulfate intravenously and orally to 44 male

and 44 female rats for 144 h. Samples of plasma, feces, urine, CO_2, all organs and whole carcass were analyzed. At 1–2 h after intravenous or oral administration, glucosamine radioactivity in plasma was bound to or incorporated into plasma proteins. After peaking at 2–4 h, radioactivity declined from plasma at a slower rate ($T1/2 = 28$ and 46 h, after IV or oral administration, respectively). Analyses of radioactivity in urine, feces and CO_2 revealed: (a) there were no gender differences; (b) about half of the radioactivity was excreted as CO_2; (c) 40% of the radioactivity was excreted in the urine; and (d) only 2% of the administered dose ended up feces indicating a high degree of glucosamine absorption. Analyses of radioactivity in tissues and organs showed that [^{14}C]-glucosamine quickly entered into all tissues including cartilage reaching a maximum at 8 h. Setnikar and Rovati (2001) concluded from these studies that the ADME data for rats and dogs are similar to the ADME data in humans, and therefore both animal models are appropriate for establishing safety of glucosamine in humans.

Glucosamine is usually taken orally and in humans 90% is absorbed (Setnikar and Rovati, 2001). Orally administered glucosamine has only 26% of the bioavailability of intravenously administered glucosamine (Barclay et al., 1998). A significant fraction of orally administered glucosamine undergoes first-pass metabolism in the liver (Barclay et al., 1998). Blood levels achieved after oral glucosamine are only 20% those achieved with intravenous glucosamine (Institute of Medicine, 2004; Setnikar and Rovati, 2001). Recent data on pharmacokinetics, bioavailability, and metabolism of glucosamine in rats (Aghazadeh-Habashi and Sattari, 2002) are similar to those reported for humans (Setnikar and Rovati, 2001).

Healthy men have serum glucosamine concentrations of ∼0.04 mmol/L when they are not consuming supplemental glucosamine (Monauni et al., 2000; Pouwels et al., 2001). Intravenous infusion of ∼9.7 g of glucosamine produced steady state serum glucosamine concentrations of ∼0.65 mmol/L (Monauni et al., 2000; Pouwels et al., 2001). Infusion of 30.45 g of glucosamine produced steady state serum glucosamine concentrations of ∼1.42 mmol/L (Monauni et al., 2000). From these concentrations we used regression analyses to estimate serum glucosamine concentrations for humans with daily intakes of usual doses (23.1 mg/kg body weight). Intake of usual oral doses of glucosamine in humans would achieve serum levels of approximately 0.06 mmol/L.
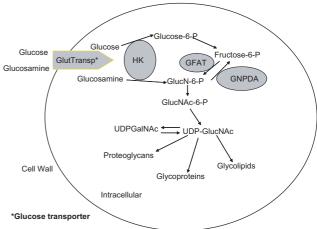
2.2. Biochemical pathways

Glucosamine is a prominent component of the hexosamine pathway, an important branch of glycolysis. Exogenous glucosamine is actively transported from

Fig. 1. Metabolic pathways of glucosamine glucose transporters are indicated by arrow and major enzymes are included in ellipses. Abbreviations are: Glucose-6-P, glucose-6-phosphate; Fructose-6-P, fructose-6-phosphate; GlucN-6-P, glucosamine-6-phosphate; GlucNAc-6-P, N-acetyl-glucosamine-6-phosphate; UDPGalNAc, uridine diphosphate (UDP)-N-acetyl-galactosamine; UDP-GlucNAc, UDP-N-acetyl-glucosamine; HK, hexokinase; GFAT, glucosamine:fructose-6-phosphate amindotransferase; and, GNPDA, glucosamine-6-phosphate deaminase.

extracellular tissue into cells by glucose transporters (Fig. 1) (Uldry et al., 2002); insulin facilitates glucosamine transport into cells (Heart et al., 2000). Glucosamine is phosphorylated by one of the family of hexokinases to glucosamine-6-phosphate (GlucN-6-P). Endogenous GlucN-6-P is formed from fructose-6-phosphate and glutamine by GlucN-6-P synthetase, commonly called glucosamine:fructose-6-P amidotransferase (GFAT) (Wu et al., 2001). GFAT irreversibly catalyzes the first and rate-controlling step in the synthesis of uridine diphosphate-N-acetylglucosamine (UDP-GlucNAc), a precursor of all macromolecules containing amino sugars. GlucN-6-P is readily converted back to fructose-6-phosphate by glucosamine-6-phosphate deaminase (GNPDA) (Wolosker et al., 1998). GlucN-6-P is acetylated to N-acetyl-glucosamine-6-P (glucNAc-6-P) by glucosamine-phosphate N-acetyltransferase and subsequently converted to UDP-GlucNAc by UDP-N-acetyl-glucosamine pyrophosphorylase. In some tissues, glucNAc-6-P is converted to glucNAc-1-P by phosphoacetylglucosamine mutase during the formation of UDP-GlucNAc (Milewski, 2002). UDP-GlucNAc can be converted to UDP-N-acetylgalactosamine (UDP-GalNAc) by UDP-N-acetylglucosamine 4-epimerase (Wu et al., 2001).

The metabolism of glucosamine is highly regulated by rates of transport into various tissues and by effects of intermediates on key enzymatic steps. For example, in many tissues the affinity of glucosamine for glucose transporters is several-fold lower than for glucose but in some mammalian tissues, the affinity of glucosa-

mine for GLUT2 transporters is higher than for glucose (Uldry et al., 2002). The affinity of the family of hexokinases in different tissues for glucosamine compared to glucose may also regulate utilization of glucosamine in various tissues. GFAT is unique among the subfamily of amidotransferase enzymes because it does not display any ammonia-dependent activity and requires glutamine as amino donor (Milewski, 2002). GFAT is strongly inhibited by the end-product of this synthetic pathway, UDP-GlucNAc (Milewski, 2002). Ambient testosterone or estrogen levels may affect tissue GFAT activity (Milewski, 2002). Between 2–5% of fructose-6-P or of the flux through the glycolytic pathway enters the hexosamine pathway via glucosamine (Milewski, 2002). In humans the endogenous production of glucosamine is in the range of 4–20 g/day or ~12 g/day (Vosseller et al., 2002; Wells et al., 2001, 2003).

3. Animal toxicity

3.1. Acute oral toxicity

Oral administration of glucosamine at very large doses (5000–15,000 mg/kg body weight) is well tolerated without documented toxicity. The LD_{50} for glucosamine for rats, mice, and rabbits exceeds 5000 mg/kg with a median value of >8000 mg/kg (Table 1). Glaza (2002) administered 5000 mg glucosamine/kg bw orally to 5 male and 5 female rats. All animals were observed clinically, twice daily, for body weight changes, mortality

Table 1
Animal toxicity from oral administration of glucosamine

Species	Strain	No.	Sex	Route of administration	Dose mg/kg	Duration, days	LD_{50} mg/kg	Significant Findings	Reference
Rat	Sprague–Dawley	na	M, F	Gavage	8000	Acute	>8000	No adverse effects reported	Setnikar et al. (1991a)
Rat	Sprague–Dawley	6	M	Oral	960	12	nd	No toxicity, decreased growth rate at high doses in weanlings	Sugimura et al. (1959)
Rat	Sprague–Dawley	5	M	Gavage	5000	15	>5000	No adverse effects reported	Glaza (2002)
		5	F	Gavage	5000	15	>5000	No adverse effects reported	
Rat	D/A (RT1^av1)	12	F	Diet	1500	52	nd**	No adverse effects reported	Beren et al. (2001)
Rat	Sprague–Dawley	8	M	Diet	300	63	nd	No adverse effects reported	Echard et al. (2001)
Rat	Spontaneously Hypertensive	8	M	Diet	300	63	nd	No adverse effects reported	Echard et al. (2001)
Rat	Sprague–Dawley	na	na	Diet	300–2700	365	nd	No adverse effects reported, NOAEL 2700 mg/kg	Setnikar et al. (1991b)
Mouse	na*	na	na	Gavage	15000	Acute	15,000		Sigma Aldrich (2001)
Mouse	CD1	na	M, F	Gavage	8000	Acute	>8000		Setnikar et al. (1991a)
Mouse	Na	na		Gavage	5000	Acute	>5000		Senin et al. (1987)
Rabbit	Na	na	na	Gavage	8000	Acute	>8000		Setnikar et al. (1991a)
Rabbit	White Danish Country	12	M	Diet	833	84	nd	No adverse effects reported	Stender and Astrup (1977)
Dog	Beagle	4	M	Diet	194	30	nd	No adverse effects reported; minor changes in hematologic and hemostatic variables noted	McNamara et al. (1996)
		6	F						
Dog	Na	na	na	Diet	159–2149	183	nd	No adverse effects reported, NOAEL 2149 mg/kg	Setnikar et al. (1991b)
Horse	Na	25	na	Diet	12	42	nd	No adverse effects reported	Hanson et al. (1967)
Horse	Yearling Quarterhorses	21	na	Diet	11	56	nd	No adverse effects reported	Fenton et al. (1999)
Horse	Standardbred	10	na	Diet	20	336	nd	No adverse effects reported	Caron et al. (2002)

***Abbreviations*: na, not available; nd, not determined.

and morbidity. After 15 days, all animals were euthanized by overexposure to carbon dioxide and subjected to macroscopic necropsy examination. The necropsy included examination of the external surface of the carcass and all organs and tissues in the thoracic, abdominal, pelvic and oral cavities. There were no test material-related effects. The acute oral LD_{50} of glucosamine HCl is greater than 5000 mg/kg.

3.2. Subchronic and chronic oral toxicity

Echard et al. (2001) examined the effects of oral administration of glucosamine hydrochloride compared to the baseline diet in 8 male spontaneously hypertensive rats (SHR) and 8 male Sprague–Dawley rats for 9 weeks. They fed 0.5% w/w in the diet or ∼300 mg/kg (which they estimated at 10–20 times the usual human dose). Samples taken included blood, heart, liver and kidneys for analytical and histological analyses. The analytical measurements included serum alanine aminotransferase, aspartate aminotransferase and blood urea nitrogen. The conclusion of this study was that there were no consistent effects on blood chemical parameters and organ histology suggesting no overall toxicity of glucosamine in this 9 week study in these two strains of rats.

In dietary studies cited by Setnikar et al. (1991b), rats ingested glucosamine sulfate at 2700 mg/kg for 52 weeks and dogs ingested 2149 mg/kg for 26 weeks. There were no treatment-related adverse effects in either species and, thus, the no adverse effects level (NOAEL) is 2700 mg/kg in rats and 2149 mg/kg in dogs (Setnikar et al., 1991b).

Studies in which rats, mice, rabbits and dogs received glucosamine orally in doses of approximately 159–8000 mg/kg/day (median dose, 867 mg/kg/day) for 12–365 days are summarized in Table 1. Oral glucosamine appears to be well tolerated by rats, mice, rabbits, dogs and horses.

3.3. Toxicity by the parenteral route

The effects of intravenous or intraperitoneal administration of glucosamine have also been examined. The LD_{50} of glucosamine in rats for intraperitoneal injection is ∼5247 mg/kg body weight and for intravenous injection is 1674 mg/kg body weight. In mice the LD_{50} of glucosamine for intraperitoneal injection is 6614 mg/kg body weight while the LD_{50} for intravenous injection is >1619 mg/kg (Setnikar et al., 1991a).

The rat model often has been selected for study because it is unusually sensitive to the effects of parenteral glucosamine administration on glucose metabolism (Institute of Medicine, 2004). The Institute of Medicine report (2004) reviews 12 reports of administration of glucosamine to rats by intravenous infusion. The doses

ranged from 240 to 9937 mg/kg body weight. Meininger et al. (2000) reported that infusion of 564 mg/kg with achieving a blood level of 0.28 mmol/l did not affect blood glucose levels. The eight other studies using average infusion rates of 2496 mg/kg detected adverse effects on glucose metabolism. The relevance of these studies to the therapeutic use of glucosamine is difficult to interpret for three reasons: first, these average doses are equivalent an oral dose of ∼9035 mg/kg body weight since oral administration of glucosamine achieves only 20% of the serum concentrations seen with parenteral administration (Setnikar and Rovati, 2001); second, the usual therapeutic dose in animals and humans is 23 mg/kg or only 0.25% of the doses used to induce alterations in glucose metabolism; and third, oral administration, contrasted to parenteral administration, of glucosamine at very high doses (300–2149 mg/kg body weight) does not affect blood glucose levels in rats (Echard et al., 2001), rabbits (Stender and Astrup, 1977), or dogs (Setnikar et al., 1991a).

3.4. In vitro studies

The Institute of Medicine Report (2004) summarized ∼40 in vitro studies using a variety of isolated, cultured and homogenized cell systems. The effects on glucose metabolism, insulin secretion, lipid metabolism, cytokine action, and cartilage function were studied. Concentrations of glucosamine ranged from 0.1 to 125 mmol/L for the low concentrations used (average, 13 mmol/L) and from 1 to 125 mmol/L for the high concentrations (average, 30 mmol/L). These average concentrations are ∼200–500 fold higher than serum concentrations that would be expected with oral administration of usual doses of glucosamine to humans—0.06 mmol/L. These model systems are not designed to assess safety but to evaluate biochemical or physiological effects of glucosamine. In certain tissues glucosamine has a higher affinity for glucose transporters than glucose (Uldry et al., 2002) and is incorporated into glycoproteins faster than glucose (Ajiboye and Harding, 1989). Glucosamine stimulates proteoglycan synthesis (Bassleer et al., 1992). Glucosamine also inhibits degradation of equine articular cartilage induced by lipopolysaccharides and interleukin 1 (Takamiya et al., 1993; Yanase et al., 1993). This supports the suggestion that exogenous glucosamine acts mainly as a substrate for biosynthesis of mucopolysaccharides and biopolymers of joints and bones (Setnikar and Rovati, 2001) and, thus, contributes to restoration of damaged cartilage (Bruyere, 2004).

Marshall et al. (1991) proposed that the insulin resistance resulting from chronic hyperglycemia might relate to increased flux of metabolites through the hexosamine biosynthetic pathway. As recently reviewed (Wells et al., 2003), many investigators have documented the effects

of increasing glucosamine concentrations on glucose transport and glycogen synthesis, predominantly in rodent muscle or adipose tissue. Increasing tissue levels of glucosamine also impair insulin secretion (Uldry et al., 2002). To assess the biological importance of these in vitro studies as they relate to intact animals, it seems important to compare the glucosamine concentrations used in vitro with those expected with in vivo use. In 11 in vitro studies related to glucose metabolism (Institute of Medicine, 2004) the average effective dose for a 50% change (ED_{50}) was ~6.6 mmol/l or >100 fold higher than expected serum levels with oral glucosamine use in humans. While ED_{50} levels for adipose tissue as low as 0.36 mmol/l have been reported (Traxinger and Marshall, 1991), levels of 25–30 mmol/l have also been reported (Heart et al., 2000). Thus, it is difficult to interpret these in vitro studies as they relate to oral administration of glucosamine for therapeutic use.

3.5. Mutagenicity data

3.5.1. In vitro studies

Glucosamine was not mutagenic in the *E. coli* reverse mutation studies of Brusick et al. (1980) However, in studies by Nanjou et al. (1984), glucosamine was found to induce strand breakage in the DNA of bacteriophage ΦX174 RF1, which the authors believed to be associated with the presence of an amino group. Using plasmid pBR322 to study structure-activity relationships in the induction of strand breakage by amino sugars, Kashige et al. (1994) reported that the addition of 100 mM D-glucosamine in Tris–HCl buffer resulted in a decrease in the amount of circular duplex plasmid DNA (ccc-DNA) and an equivalent increase in the amount of nicked open-circular plasmid DNA (oc-DNA). The authors suggest that introduction of acidic groups as sulfate and phosphate at the six position of the molecule is responsible for the DNA-breaking activity of D-glucosamine. They also suggested that an active oxygen species and/or D-glucosamine radicals generated in the process of autoxidation of the amino sugar were involved in the DNA strand breakage (Kashige et al., 1991), a possibility supported by the electron spin resonance analyses of glucosamine by Yamaguchi et al. (1998).

In unpublished studies performed by Cargill, the mutagenic activity of glucosamine HCl (REGENA-SURE™*serif*) was evaluated in the *Salmonella–Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay (Mecchi, 2003). Tester strains used in the mutagenicity assay were *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain *WP2uvrA*. The assay was conducted with five concentrations of glucosamine HCl in both the presence and absence of microsomal enzymes prepared from Aroclor™-induced rat liver (S9 mix), along with vehicle and positive controls using three plates per dose. Concentrations tested with all tester strains were 100, 333, 1000, 3330, and 5000 μg per plate or concentrations of ~0.53–26.5 mmol/L. Results from this assay indicate that under the conditions of this study, glucosamine HCl did not cause a positive increase in the mean number of revertants per plate with any of the tester strains. These test results indicate that glucosamine is not mutagenic (Mecchi, 2003).

3.5.2. In vivo studies

The effect of D-glucosamine on bone marrow chromosomes was examined in mice by Banerjee and Manna (1984). Glucosamine HCl (10 mg/kg body weight) was administered to Swiss albino mice via intraperitoneal injection. Bone marrow chromosome aberrations were assessed at 12 different intervals between 10 min and 30 days and compared to mice injected with distilled water as controls. Whereas chromosome aberrations in control bone marrow samples were negligible, there was a significant increase in chromosome aberration frequency in samples from mice treated with glucosamine. The nonrandom distribution of chromatid breaks within the chromosomes led the authors to speculate these might be due to some physicochemical stress at inherently weaker regions in the chromosomes. Manna et al. (2004) also examined the micronuclei of five exotic fish injected intraperitoneally with glucosamine HCl at 10 mg/kg body weight. The percentage of micronuclei was slightly but not significantly higher in glucosamine injected fish than in controls.

A mouse micronucleus assay was conducted to evaluate clastogenic activity and/or disruption of the mitotic apparatus by glucosamine hydrochloride by detecting micronuclei in polychromatic erythrocyte (PCE) cells in Crl: CD-1®(ICR) BR mouse bone marrow (Cantox Report, 2001). The high dose of 2000 mg/kg selected for this study was based on relevant acute toxicity information (refer Section 3.1). It is also the maximum allowable dose in various regulatory guidelines. For the micronucleus assay, glucosamine hydrochloride was mixed with cell culture grade water and dosed by oral gavage to six males per dose level (500, 1000, or 2000 mg/kg) for each scheduled harvest time point. Five animals per group per harvest time point were euthanized approximately 24 or 48 h after dosing for extraction of the bone marrow. At least 2000 PCEs per animal were analyzed for the frequency of micronuclei. Cytotoxicity was assessed by scoring the number of PCEs and normochromatic erythrocytes (NCEs) in at least the first 500 erythrocytes for each animal. Glucosamine HCl did not induce signs of clinical toxicity in any of the treated animals at up to 2000 mg/kg. Glucosamine did not induce any statistically significant increases in micronucleated PCEs at any dose level examined.

Glucosamine HCl was not cytotoxic to the bone marrow at any dose level tested (i.e., no statistically significant decrease in the PCE:NCE ratios were observed). Glucosamine HCl was negative in the mouse bone marrow micronucleus assay under the conditions of this assay.

4. Human clinical studies

4.1. Clinical trial selection

For human clinical studies the relevant articles were identified by Medline search and by review of articles referenced in primary reports and review articles. Detailed literature searches were performed previously (Institute of Medicine, 2004) and in three meta-analyses (McAlindon et al., 2000; Richy et al., 2003; Towheed et al., 2004). For this current review, articles from these four previous reports were reviewed and a Medline search was performed for the years 2000–2003 using these key words, glucosamine and humans. We reviewed references of all relevant articles for additional references. Articles included in this review relate to glucosamine administration to humans for investigational or therapeutic purposes. Relevant data were extracted and tabulated. Semiquantitative and statistical analyses of data were performed (Anderson et al., 1995, 1999).

The total number of patients represents the sum of all patients studied or the sum of all patients who had the specific measure described. The weighted average number of weeks for patients was calculated as follows: sum of (number of patients in each trial times number of weeks in each individual trial) divided by total number of patient in all studies. The ratio of side effects from glucosamine or placebo was calculated as follows: number of patients treated with glucosamine with side effects divided by number of patients treated with placebo with side effects. The average ratio of side effects in each study for glucosamine and placebo was averaged, the standard error of these values calculated, and the 95% upper and lower confidence interval were calculated. Side effects with NSAID were calculated in a similar manner.

Since three meta-analyses (McAlindon et al., 2000; Richy et al., 2003; Towheed et al., 2004) have carefully evaluated efficacy, we tabulated reported outcomes and used simple arithmetic means and median values to characterize the primary reports. The P-value reported represents the median of P-values reported for each individual study since many studies had multiple P-values reported. When a significance difference was reported but the P-value was not provided, a value of 0.05 was assigned. When values were not clinically significant, a value of 0.1 was assigned; this is justified because these studies reported favorable trends in effi-

cacy or significant values for some outcome measures. The average P-value is simply the average of reported P-values. Five studies included comparisons of glucosamine to ibuprofen. These values are reported as percentages of patients who developed side effects in these two groups.

4.2. Characteristics of clinical studies

Thirty-three studies of chronic glucosamine administration were included in this analysis (Table 2). This includes data on 3063 patients treated with glucosamine for a weighted average of 17 weeks (range 3–156). Twenty-eight studies used a randomized, controlled trial (RCT) design, one study was controlled and five studies were observational. Twenty-seven studies used glucosamine alone, five included chondroitin sulfate and two included other supplements in the test preparation. Seven studies were comparator trials in which glucosamine was compared to other agents (ibuprofen in five studies, phenylbutazone in one study and piroxicam in one study). Twenty-nine studies used oral therapy exclusively, one used intramuscular administration alone, and three used oral administration in conjunction with intravenous, intramuscular, or intra-articular administration. Two short-term studies (Monauni et al., 2000; Pouwels et al., 2001) were reviewed to assess glucose metabolism. Four studies, one on skin wrinkles (Murad and Tabibian, 2001) and three on temporomandibular joint complaints (Nguyen et al., 2003; Shankland, 1998; Thie et al., 2001) were included to make the safety assessment as comprehensive as possible.

4.3. Effects of glucosamine on glucose metabolism in humans

In two acute metabolic ward studies (Monauni et al., 2000; Pouwels et al., 2001), large amounts of glucosamine—~7.2 g or 9.7 g of the glucosamine free base—were infused over 5 h with no change in blood glucose values. Sixteen chronic studies have evaluated fasting plasma glucose values. Fasting blood glucose values decreased non-significantly from 92.9 to 89.9 mg/dl for values reported from five trials (Table 3). The Reginster study enrolled 108 subjects and followed them for 3 years; they reported that blood glucose values were slightly lower than baseline values (Reginster et al., 2001). Scroggie et al. (2003) measured glycosylated hemoglobin (HbA$_{1c}$) and blood glucose values in 22 diabetic and 12 control subjects over 90 days and noted no significant changes. Tannis et al. (2004) reported that daily administration of 1500 mg glucosamine sulfate over 12 weeks was associated with no significant changes in fasting plasma glucose or insulin values or oral glucose tolerance test. Yu et al. (2003) reported that administration of 1500 mg glucosamine for 28 days had no

Table 2
Human clinical trial summary

Study	Type study	Glucosamine form	Other treatment	Route*	Dose mg/d	No. of subjects	Duration days
Almada et al. (2000)	RCT	SO$_4$	None	Oral	1500	6	84
Braham et al. (2003)	RCT	HCl	None	Oral	2000	25	84
D'Ambrosio et al. (1981)	RCT	SO$_4$	None	Oral/iv/im	1500	15	21
Das and Hammad (2000)	RCT	HCl	CHS	Oral	2000	46	192
Drovanti et al. (1980)	RCT	SO$_4$	None	Oral	1500	40	30
Forster et al. (1996)	RCT	SO$_4$	None	Oral	1500	78	90
Giordano et al. (1996)	Observational	SO$_4$	None	Oral	1500	20	365
Houpt et al. (1999)	RCT	HCl	None	Oral	1500	45	147
Hughes and Carr (2002)	RCT	SO$_4$	None	Oral	1500	39	168
Leffler et al. (1999)	RCT	HCl	CHS, Mn	Oral	1500	31	112
Muller-Fabbender et al. (1994)	RCT-C	SO$_4$	Vs. ibuprofen	Oral	1500	100	28
Mund-Hoym (1980)	Controlled	SO$_4$	Vs. phenylbutazone	Oral/im	1000	40	32
Murad and Tabibian (2001)	Controlled	SO$_4$	Supplement	Oral	Uncert	57	35
Nguyen et al. (2003)	RCT	HCl	CHS	Oral	1500	19	84
Noack et al. (1994)	RCT	SO$_4$	None	Oral	1500	120	28
Pavelka et al. (2002)	RCT	SO$_4$	None	Oral	1500	84	1095
Pujalte et al. (1980)	RCT	SO$_4$	None	Oral	1500	11	49
Qui et al. (1998)	RCT-C	SO$_4$	Vs. ibuprofen	Oral	1500	88	28
Reicheit et al. (1994)	RCT	SO$_4$	None	IM	114	73	42
Reginster et al. (2001)	RCT	SO$_4$	None	Oral	1500	87	1095
Rindone et al. (2000)	RCT	SO$_4$	None	Oral	1500	49	60
Rovati (1997)	RCT-P-C	SO$_4$	Vs. piroxicam	Oral	1500	80	150
Rovati (1992), study 1	RCT	SO$_4$	None	Oral	1500	123	28
Rovati (1992), study 2	RCT	SO$_4$	None	Oral	1500	76	42
Rovati (1992), study 3	RCT-C	SO$_4$	Vs. ibuprofen	Oral	1500	100	28
Scroggie et al. (2003)	RCT	HCl	CHS	Oral	1500	22	90
Shankland (1998)	Observational	HCl	CHS	Oral	3200	50	35
Tannis et al. (2004)	RCT	SO$_4$	None	Oral	1500	11	84
Tapadinhas et al. (1982)	Observational	SO$_4$	None	Oral	1500	1367	50
Thie et al. (2001)	RCT-C	SO$_4$	Vs. ibuprofen	Oral	1500	22	90
Yu et al. (2003)	Observational	SO$_4$	None	Oral	1500	12	28
Vajranetra (1984)	Observational	SO$_4$	None	Oral/ia	1500	108	84
Vas (1982)	RCT-C	SO$_4$	Vs. ibuprofen	Oral	1500	19	56

*Abbreviations: RCT, randomized controlled trial; C, comparator; P, placebo; CHS, chondrotin sulfate; iv, intravenous; im, intramuscular; ia, intraarticular.

effect on glucose tolerance or insulin sensitivity of 10 non-diabetic subjects. In total, reports from 16 trials including 854 subjects followed for a weighted average of 37 weeks indicated that there were no significant changes in blood glucose values. For the entire group of 33 chronic studies of predominantly older subjects, three developed diabetes with placebo treatment and two developed diabetes with glucosamine treatment.

4.4. Objective measures of safety

In two metabolic ward studies, volunteers have received large doses of glucosamine intravenously over 300 min. Pouwels et al. (2001) intravenously infused ~7.2 g of glucosamine as the sulfate salt over a 300 min period into 10 healthy volunteers. This was well tolerated and not associated with reported side effects. Monauni et al. (2000) intravenously infused 9.7 g of glucosamine over a 300 min period into 10 healthy volunteers. Again this was well tolerated with no reported

side effects. When they subsequently intravenously infused 30.5 g of glucosamine—achieving plasma levels >20-fold higher than would be expected with usual doses of oral glucosamine—into five healthy volunteers, this dose was well tolerated by four subjects and only one had symptoms—he developed a headache.

Thirteen studies reported specific safety measures including some of these assessments: chemistry panel including liver and kidney safety assessments, hematologic values (white blood count, red blood count, hemoglobin, and platelet count), urinalyses, occult blood measurements of stool, and cardiovascular parameters including blood pressure and pulse rate (Table 3). None of the studies reported adverse effects on these measurements from glucosamine administration. In general these safety reports included >800 subjects treated for a weighted average of ~40 weeks. Specifically the number of studies assessing various parameters were as follows: chemistry panel, 12; hematologic parameters, 13; urinalyses, 10; occult blood in stool, 3; and cardiovascu-

Table 3
Evaluation of fasting plasma glucose and safety parameters

Study	Glucose before	mg/dl after	Summary	Blood chem	CBC	UA	Occult blood	BP P	Side effects GluN/P
Almada et al. (2000)	94	94		NA	NA	NA	NA	NA	NA
Braham et al. (2003)	NA			NA	NA	NA	NA	NA	1.10
D'Ambrosio et al. (1981)	109	97		NCS	NCS	NCS	NA	NCS	1.00
Das and Hammad (2000)	NA			NA	NA	NA	NA	NA	0.89
Drovanti et al. (1980)	82	82		NCS	NCS	NA	NCS	NA	0.83
Forster et al. (1996)	NA			NA	NA	NA	NA	NA	0.20
Giordano et al. (1996)	NCS			NCS	NCS	NCS	NA	NA	1.00
Houpt et al. (1999)	NA			NA	NA	NA	NA	NA	1.00
Hughes and Carr (2002)	NCS			NCS	NCS	NCS	NA	NA	0.90
Leffler et al. (1999)	NA			NA	NCS	NA	NCS	NCS	0.97
Muller-Fabbender et al. (1994)	NA			NA	NA	NA	NA	NCS	NA
Nguyen et al. (2003)	NA			NA	NA	NA	NA	NA	1.43
Noack et al. (1994)	NCS			NCS	NCS	NCS	NA	NCS	0.62
Pavelka et al. (2002)	NCS			NCS	NCS	NCS	NA	NA	0.56
Pujalte et al. (1980)	NA			NCS	NCS	NCS	NA	NA	0.00
Qui et al. (1998)	NA			NCS	NCS	NCS	NA	NA	NA
Reginster et al. (2001)	Slightly lower			NCS	NCS	NCS	NA	NCS	0.82
Rindone et al. (2000)	NA			NA	NA	NA	NA	NA	0.50
Rovati (1997)	NA			NA	NA	NA	NA	NA	0.62
Rovati (1992), study 1	NA			NCS	NCS	NCS	NA	NA	0.62
Rovati (1992), study 2	NA			NCS	NCS	NCS	NA	NA	0.71
Rovati (1992), study 3	NA			NCS	NCS	NCS	NA	NA	NA
Scroggie et al. (2003)	HbA1c	NCS		NA	NA	NA	NA	NA	NA
Tannis et al. (2004)	82.3	79.2		NA	NA	NA	NA	NA	NA
Yu et al. (2003)	97.2	97.2		NA	NA	NA	NA	NA	NA
Vas (1982)	NA			NA	NCS	NA	NCS	NCS	NA
Average	92.9	89.9							0.76
No. with reports	5		16	12	13	10	3	6	18
Total patients	84	854	803	826	736	90	372	988
Weighted average no. of weeks	5.6	37.2	38.9	38.6	41.7	9.1	40.7	37.2

Abbreviations: NA, not available; NCS, not clinically significant; HbA1c, glycosylated hemoglobin; chem., chemistry; UA, urinalysis; occult blood, stool measurement; BP, blood pressure; P, pulse; GlucN/P, ratio of side effects from glucosamine divided by those from placebo.

lar parameters, 6. Blood pressure and pulse rate were monitored continuously for the 21 subjects who had large amounts of glucosamine infused intravenously with no reported adverse effects (Monauni et al., 2000; Pouwels et al., 2001). None of the studies reported significant changes in these parameters.

4.5. Common symptoms with placebo, glucosamine and NSAID

Nonspecific symptoms are commonly reported in clinical trials. In a 3-year study, 93% of subjects receiving placebo reported symptoms (Reginster et al., 2001). The most common symptoms reported with placebo or glucosamine were: mild gastrointestinal symptoms including constipation, diarrhea, nausea, dyspepsia, excessive gas, abdominal distension, and abdominal cramps; headache; and skin rash or pruritis. Eighteen chronic studies that provided side effect data comparing glucosamine to placebo were analyzed (Table 3). The contents of the placebo capsules used in these studies were: not stated, in 9 studies; lactose, in 3; excipients, in 3; inert material, in 1; calcium carbonate, in 1; and

50% maltodextrin and 50% whey protein, in 1. These studies included 988 subjects followed for a weighted average of 37 weeks. In 13 of the 18 studies, symptoms were reported less commonly in glucosamine-treated subjects than in placebo-treated subjects. The ratio of symptoms for glucosamine compared to those for placebo is presented for each study. The placebo has a score of 1.0 and the frequency of symptoms with glucosamine is a fraction of this. When the frequency of symptoms is the same the ratio for glucosamine is 1.0. When less symptoms are reported for glucosamine than placebo, the ratio is less than 1.0. Only two studies reported that symptoms were more common with glucosamine than placebo. The frequency of symptoms with glucosamine ranged from none (0.0) to 143% (1.43) of those reported for placebo. The average for the ratio of symptoms for glucosamine compared to placebo was 0.76 (95% confidence interval, 0.61–0.92). This suggests that symptoms were 24% less common with glucosamine than placebo and that this was statistically significant. Richy et al. (2003), in their meta-analysis, indicated that the adverse effect rate with glucosamine was 20% lower than placebo.

The Institute of Medicine Report (2004) summarizes case reports and other adverse events occurring with glucosamine use. This report concludes that: "Human studies show an equal incidence of mild, transient adverse effects in placebo control groups and glucosamine groups." (p. 4, 2004)

Five studies compared side effects of glucosamine with ibuprofen, the most commonly used non-steroidal anti-inflammatory drug (NSAID) for arthritis. The prevalence of side effects in patients using glucosamine was 10.0% compared to 32.5% for patients using ibuprofen. The Institute of Medicine (2004) report also concluded that side effects were less common with glucosamine than with ibuprofen.

4.6. Assessment of efficacy

The efficacy of glucosamine for arthritic complaints has been extensively studied and three recent meta-analyses (McAlindon et al., 2000; Richy et al., 2003; Towheed et al., 2004) that critically review randomized controlled trials (RCTs) are available. McAlindon et al. (2000) conclude that glucosamine was moderately efficacious for relief of arthritic complaints. Richy et al. (2003) conclude that glucosamine had highly significant efficacy on all aspects of knee osteoarthritis including joint space narrowing, pain, and mobility scores. Towheed et al. (2004) report that "In the 13 RCTs in which

glucosamine was compared to placebo, glucosamine was found to be superior in all RCTs, except one. In the four RCTs in which glucosamine was compared to an NSAID, glucosamine was superior in two and equivalent in two." In our current evaluation 23 clinical studies of patients with osteoarthritis were reviewed (Table 4); this does not include the three studies of temporo-mandibular joint (TMJ) symptoms. Twelve studies reported significant differences and included *P*-values (from 0.05 to 0.001). Seven indicated that significant improvement was seen but did not provide *P*-values; a *P*-value of 0.05 was assigned to these studies. Only three studies indicated that no significant difference was seen and two noted a slight improvement with glucosamine administration; a *P*-value of 0.1 was assigned to these studies since they reported favorable but not quite statistically significant results. The average of all reported and imputed *P*-values for the 22 studies was 0.040 and the median *P*-value was 0.05. While a detailed analysis of efficacy was not undertaken, this survey indicates that glucosamine administration, at a dose of 1500 mg/day, is moderately effective in decreasing arthritic complaints.

5. Discussion

Glucosamine has been extensively studied in animals and humans. Acute studies in animals indicate that very large doses (5000–15,000 mg/kg) can be administered orally without evidence of toxicity; the LD_{50} in rats and mice is >8000 mg/kg. Subacute and chronic studies in rats, mice, rabbits and dogs received glucosamine orally in doses of approximately 159–2700 mg/kg/day for 12–365 days and no adverse effects were noted; the NOAEL for rats is 2700 mg/kg and for dogs is 2149 mg/kg. This compares to the usual dose for humans of ∼23 mg/kg.

The entry of glucosamine into cells is stimulated by insulin and involves the glucose-transporter system (Heart et al., 2000; Pouwels et al., 2001). Glucosamine is then phosphorylated to glucosamine-6-phosphate by tissue hexokinases (Monauni et al., 2000; Pouwels et al., 2001). These intermediary metabolism pathways are finely regulated as indicated by the following observations: (1) glucose-6-phosphate is a potent inhibitor of most hexokinases and glucosamine-6-phosphate is a weak inhibitor of this family of enzymes (Nelson et al., 2000); (2) glucosamine inhibits the glucose transporter system (e.g., GLUT-4) further limiting its entry into cells (Nelson et al., 2000); (3) glucosamine inhibits GFAT activity, limiting formation of glucosamine-6-phosphate from fructose-6-phosphate; (4) glucosamine-6-phosphate is converted to fructose-6-phosphate by glucosamine-6-phosphate deaminase, preventing excessive flux through this relatively minor metabolic pathway (Wolosker et al., 1998); and (5) when free glucosamine enters cells, its downstream metabolism is

Table 4
Overview of efficacy of glucosamine for arthritic complaints

Study	Joints evaluated	Arthritis symptoms significant difference
Braham et al. (2003)	Knees	0.038
D'Ambrosio et al. (1981)	Generalized OA	0.01
Das and Hammad (2000)	Knees	0.04
Drovanti et al. (1980)	Generalized OA	0.005
Forster et al. (1996)	Knees	Sign. diff. (0.05)
Giordano et al. (1996)	Generalized OA	0.001
Houpt et al. (1999)	Knees	NCS (0.1)
Hughes and Carr (2002)	Knees	NCS (0.1)
Leffler et al. (1999)	Knees or back	0.02
Muller-Fabbender et al. (1994)	Knees	Sign. diff. (0.05)
Mund-Hoym (1980)	Back	Sign. diff. (0.05)
Noack et al. (1994)	Knees	0.05
Pavelka et al. (2002)	Knees	0.01
Pujalte et al. (1980)	Generalized OA	0.01
Qui et al. (1998)	Knees	Sign. diff. (0.05)
Reicheit et al. (1994)	Knees	Sign. diff. (0.05)
Reginster et al. (2001)	Knees	Sign. diff. (0.05)
Rindone et al. (2000)	Knees	NCS (0.1)
Rovati (1997)	Knees	Sign. diff. (0.05)
Rovati (1992), study 1	Knees	0.014
Rovati (1992), study 2	Knees	0.012
Tapadinhas et al. (1982)	Generalized OA	0.001
Vajranetra (1984)	Knees	Sign. diff. (0.05)

Abbreviations: NA, not applicable; OA, osteoarthritis; NA, not available; NCS, not clinically significant.

significantly limited by one or two steps distal to its phosphorylation. The conversion of glucosamine-6-phosphate to *N*-acetyl-glucosamine-6-phosphate and then further conversion to UDP-*N*-acetylglucosamine-6-phosphate, specifically, are limited (Nelson et al., 2000). Thus, it appears very unlikely that cellular metabolites of free glucosamine would exceed physiologic levels after oral glucosamine intake (Reicheit et al., 1994).

The effects of glucosamine on glucose metabolism have interested laboratory investigators for many years because pharmacologic concentrations of glucosamine affect insulin action and secretion. Glucosamine is a common metabolic product in most tissues of the body and is incorporated into glycosaminoglycans (Setnikar and Rovati, 2001). Setnikar and Rovati (2001) reviewed the metabolism of glucosamine in humans and these data can be summarized. Glucosamine sulfate or hydrochloride salts are dissociated in the stomach and free glucosamine enters the small intestine where 90% is absorbed. Much of the glucosamine is metabolized in the first pass through the liver. The blood level of glucosamine after oral administration approximates 20% of that observed with intravenous administration. Glucosamine is taken up by cells by glucose transporter proteins but the affinity of glucosamine for these transporters is substantially lower than that of glucose (Nelson et al., 2000). Thus, it seems likely that the concentration of glucosamine in most cells would be substantially lower than that in plasma. With intravenous administration of 9.7 g over 5 h, serum glucosamine concentrations of 0.7 mmol/l were achieved (Monauni et al., 2000). With administration of 500 mg in three divided doses it seems unlikely that serum concentrations above 0.06 mmol/l would be achieved. In 11 relevant in vitro studies examining the effects of glucosamine on glucose metabolism the glucosamine concentrations ranged from 0.1 to 50 mmol/l (Heart et al., 2000; Institute of Medicine, 2004; Nelson et al., 2000; Sakai and Clemmons, 2003). The effective dose for a 50% change (ED_{50}) for a wide range of regulatory activities for glucose metabolism averaged 6.6 mmol/l or >100-fold higher than expected serum concentrations in humans with usual doses of oral glucosamine. For example, the ED_{50} for insulin-stimulated glucose uptake in isolated fat cells is 25–30 mmol/l (Heart et al., 2000). Thus, it seems very unlikely that oral administration of 1500 mg/d (23.1 mg/kg, the commonly used amount) to 3200 mg/d (49.2 mg/kg, an amount used in one chronic study) of glucosamine would have a discernable effect on metabolic pathways involved in glucose metabolism in humans.

Because the blood level achieved with intravenous glucosamine is approximately five-fold higher than with oral administration (Setnikar and Rovati, 2001), it appears that humans can easily tolerate more than 9.7 g/day. The tolerable daily intake of glucosamine was calculated as follows. Humans tolerate more than 9.7 g of free-base glucosamine. We assumed that these young men have average weights of ∼70 kg. The calculation of mg/kg is as follows: 9700 mg divided by 70 kg is >138 mg/kg/day of the free base glucosamine. Because glucosamine hydrochloride provides 83% free base, humans tolerate >166 mg/kg/day (138 divided by 0.83) of glucosamine hydrochloride. Furthermore, since only 90% of glucosamine is absorbed (Setnikar et al., 1993), humans tolerate >184 mg/kg/day (166 divided by 0.9) of the glucosamine hydrochloride. Our conservative recommendation is that a tolerable daily intake of glucosamine is 184 mg/kg/day.

From the estimates of endogenous glucosamine production, 2–5% of ingested carbohydrate (Milewski, 2002), it appears that endogenous production would far exceed the levels of ingested glucosamine. With intakes of 200–350 g of carbohydrate, humans would produce an estimated 4–20 g of glucosamine per day (∼12 g/day) (Vosseller et al., 2002). With the intake of 0–1.5 g of oral glucosamine daily, blood levels would be equivalent to infusing 20% of this amount (Institute of Medicine, 2004; Setnikar and Rovati, 2001), or 0.3 g per day. Furthermore, when large amounts of carbohydrate are ingested chronically, insulin sensitivity improves in healthy subjects (Anderson et al., 1973) and in diabetic subjects (Anderson, 1977). For example, when we fed 80% of energy as carbohydrate (∼400 g of carbohydrate) to healthy volunteers for 11–13 weeks, they had improved glucose tolerance and insulin sensitivity (Anderson et al., 1973) despite estimated endogenous production of 8–20 g of glucosamine per day. Thus, in humans, it seems unlikely when providing 1.5 g of exogenous glucosamine—with anticipated metabolic effects on liver and peripheral tissues of only 20–26% (0.3–0.4 g) (Institute of Medicine, 2004; Setnikar and Rovati, 2001) of this–that adverse effects on glucose metabolism or insulin sensitivity in humans will be seen.

Because of the effects of large concentrations of glucosamine on glucose metabolism in animal and in vitro models, we rigorously examined the available data related to this question in humans. In clinical trials there is no evidence that glucosamine in usual doses affects fasting plasma glucose concentrations. In two clinical trials (Tannis et al., 2004; Yu et al., 2003) glucosamine administration had no effect on estimates of insulin sensitivity and in one study (Scroggie et al., 2003) glucosamine intake had no effect on glycemic control of diabetic subjects. Finally, when large amounts of glucosamine (7.2 or 9.7 g) were infused into healthy volunteers, no adverse effects on blood glucose concentrations were observed over the 5-h period of study (Monauni et al., 2000; Pouwels et al., 2001).

In reviewing human clinical trials we tabulated data on efficacy of glucosamine administration on symptoms of osteoarthritis. Our observations are consistent with those from three rigorous meta-analyses (McAlindon

et al., 2000; Richy et al., 2003; Towheed et al., 2004). Individuals with osteoarthritis of the knee or spine have significantly less symptoms while taking glucosamine than those taking placebo. McAlindon et al. (2000) conclude that glucosamine is moderately efficacious for relief of symptoms of osteoarthritis. Richy et al. (2003) conclude that glucosamine has highly significant effects on all aspects of knee osteoarthritis. Two recent randomized clinical trials (Bruyere, 2004) included 414 women followed for three years. These studies documented an increase in joint space with glucosamine treatment while there was a decrease in the placebo group; the differences were significant ($P < 0.001$).

To evaluate safety for humans, we reviewed data from 32 clinical trials including 3073 individuals treated with glucosamine for periods of 3–156 weeks (weighted average, 17 weeks). We concur with the conclusions of the Institute of Medicine (2004) that mild, transient side effects were seen in both placebo and glucosamine treated individuals. Our analysis of side effects suggests that they were significantly (24%) less frequent in glucosamine-treated individuals than in placebo-treated individuals; Richy et al. (2003) calculated that side effects are 20% less common in glucosamine-treated subjects than in the placebo groups.

NSAID are widely used for relief of osteoarthritic symptoms with >110 million prescriptions and drug costs of $4.8 billion annually in the US; these estimates do not include over-the-counter purchases (Laine, 2001). In 1997 the estimated deaths from NSAID-related gastrointestinal adverse events in the US was 16,500 (Wolfe et al., 1999). NSAID with specific COX-2 inhibitory action have lower gastrointestinal side effects than other NSAID (Silverstein et al., 2000) but are associated with higher rates of hypertension and cardiovascular complications (Mukherjee et al., 2001; Solomon et al., 2004). In contrast, the Institute of Medicine (2004) carefully reviewed reported adverse events reported for glucosamine and noted three adverse events reports (Special Nutritionals Adverse Event Monitoring System) and three clinical case reports. Furthermore, our analysis and that of the Institute of Medicine (2004) indicate that side effects from glucosamine are less than one third those from ibuprofen, a widely used NSAID. All the available data indicate that glucosamine and NSAID have similar efficacy but that glucosamine has substantially less toxicity.

6. Conclusions

Oral glucosamine administration is well tolerated by animals and humans. Glucosamine had been orally administered to rats, mice, rabbits, dogs and horses in more than 17 reported studies. The estimated LD_{50} for oral glucosamine administration is as follows: for rats,

>5000 mg/kg; for mice, >8000 mg/kg; and for rabbits, >8000 mg/kg. In 13 animal subacute or chronic studies, daily doses of 194–2700 mg/kg body weight were administered for 12–365 days and there were no treatment-related adverse effects reported. Many in vitro studies used glucosamine with average low concentration of 13 mmol/l and average high concentrations of 30 mmol/l. ED_{50} calculations for glucosamine effects on glucose metabolism averaged 6.6 mmol/l. Since the cellular concentration of glucosamine with usual doses in humans is estimated at 0.06 mmol/l, these ED_{50} estimations are >100-fold higher than expected tissue levels with usual therapeutic doses.

To examine possible toxic effects in humans, results from 32 clinical trials with glucosamine were reviewed. These trials included 3063 subjects studied for an average of 17 weeks. While there have been concerns originating from in vitro studies and intravenous administration to rodents that glucosamine might adversely affect glucose metabolism, careful studies in humans show no adverse effects on glucose homeostasis. Overall, 16 studies including 854 subjects for 37 weeks reported no adverse effects on glucose metabolism. Glucosamine is well tolerated by humans for periods of up to three years. While the usual dose is 1500 mg/day in three doses, doses of up to 3200 mg/day were well tolerated. Healthy young subjects had no adverse effects from infusion of 9.7 g and only one of five developed a headache when 30.5 g was infused. This suggests that humans tolerate intake of at least 184 mg/kg/day of glucosamine daily. In 13 clinical trials reporting safety information there were no adverse effects of glucosamine on blood chemistries, hematologic parameters, urinalysis, occult blood in feces, or cardiovascular parameters. Symptoms or side effects were reported significantly less frequently with glucosamine than with placebo. Reported side effects were 24% less common in subjects treated with glucosamine than with placebo. Finally, glucosamine appears to be moderately to highly effective in decreasing symptoms resulting from osteoarthritis.

References

Aghazadeh-Habashi, A., Sattari, S., 2002. Single dose pharmacokinetics and bioavailability of glucosamine in the rat. Journal of Pharmacological Sciences 5, 181–184.

Ajiboye, R., Harding, J.J., 1989. The non-enzymatic glycosylation of bovine lens proteins by glucosamine and its inhibition by aspirin, ibuprofen and glutathione. Experimental Eye Research 49, 31–41.

Almada, A.L., Harvey, P.W., Platt, P.J., 2000. Effect of chronic oral glucosamine sulfate upon fasting insulin resistance index (FIRI) in nondiabetic individuals. FASEB Journal 14, A750-abstract.

Anderson, J.W., 1977. Effect of carbohydrate restriction and high carbohydrate diets on men with chemical diabetes. American Journal of Clinical Nutrition 30, 402–408.

Anderson, J.W., Herman, R.H., Zakim, D., 1973. Effect of high glucose and high sucrose diets on glucose tolerance of normal men. American Journal of Clinical Nutrition 26, 600–607.

Anderson, J.W., Johnstone, B.M., Cook-Newell, M.E., 1995. Meta-analysis of effects of soy protein intake on serum lipids in humans. New England Journal of Medicine 333, 276–282.

Anderson, J.W., Johnstone, B.M., Remley, D.T., 1999. Breast-feeding and cognitive function: a meta-analysis. American Journal of Clinical Nutrition 70, 525–535.

Banerjee, G., Manna, G.K., 1984. Bone marrow chromosome aberrations in mice injected with an antimetabolite, D-glucose amine hydrochloride. Perspectives in Cytology and Genetics 4, 377–382.

Barclay, T.S., Tsourounis, C., McCart, G.M., 1998. Glucosamine. Annals of Pharmacotherapy 32, 574–579.

Bassleer, C., Henrotin, Y., Franchimont, P., 1992. In-vitro evaluation of drugs proposed as chondroprotective agents. International Journal of Tissue Reactions 14, 231–241.

Beren, J., Hill, S.L., Diener-West, M., Rose, N.R., 2001. Effect of preloading oral glucosamine HCl/chondroitin sulfate/manganese ascorbate combination on experimental arthritis in rats. Proceedings of the Society for Experimental Biology and Medicine 226, 144–151.

Braham, R., Dawson, B., Goodman, C., 2003. The effect of glucosamine supplementation on people experiencing regular knee pain. British Journal of Sports Medicine 37, 45–49.

Brusick, D.J., Simmons, V.F., Rosenkrantz, H.S., Ray, V.A., Stafford, R.S., 1980. An evaluation of the *Escherichia coli* WP2 and WP2 UVRA reverse mutation assay. Mutation Research 76, 169–190.

Bruyere, O., 2004. Glucosamine has a disease-modifying effect on osteoarthritis. Menopause 11, 138–143.

Cantox Report, 2001. Glucosamine: GRAS status evaluation. Bridgewater, NJ.

Caron, J.P., Peters, T.L., Hauptman, J.G., Eberhart, S.W., Orth, M.W., 2002. Serum concentrations of keratan sulfate, osteocalcin, and pyridinoline crosslinks after oral administration of glucosamine to standardbred horses during racing training. American Journal of Veterinary Research 63, 1106–1110.

D'Ambrosio, E., Casa, B., Bompani, R., Scali, G., Scali, M., 1981. Glucosamine sulfate: a controlled clinical investigation in arthrosis. Pharmacotherpeutica 2, 504–508.

Das Jr., A., Hammad, T.A., 2000. Efficacy of a combination of FCHG49(TM) glucosamine hydrochloride, TRH122(TM) low molecular weight sodium chondroitin sulfate and manganese ascorbate in the management of knee osteoarthritis. Osteoarthritis and Cartilage 8, 343–350.

Drovanti, A., Bigamini, A.A., Rovati, A.L., 1980. Therapeutic activity of oral glucosamine sulfate in osteoarthrosis: A placebo-controlled double-blind investigation. Clinical Therapeutics 3, 260–272.

Echard, B.W., Talpur, N.A., Funk, K.A., Bagchi, D., Preuss, H.G., 2001. Effects of oral glucosamine and chondroitin sulfate alone and in combination on the metabolism of SHR and SD rats. Molecular and Cellular Biochemistry 225, 85–91.

Fenton, J.L., Orth, M.W., Chlebek-Brown, K.A., Nielsen, B.D., Corn, C.D., Waite, K.S., Caron, J.P., 1999. Effect of longeing and glucosamine supplementation on serum markers of bone and joint metabolism in yearling quarter horses. Canadian Journal of Veterinary Research 63, 288–291.

Forster, K., Schmid, K., Rovati, L., Giacovelli, G., Dreiser, R., Bourgeois, P., 1996. Longer-term treatment of mild-to-moderate osteoarthritis of the knee with glucosamine sulfate. European Journal of Clinical Pharmacology 50, 542-abstract.

Giordano, N., Nardi, P., Senesi, M., Palumbo, F., Battisti, E., Gonnelli, S., Franci, B., Campagna, M.S., Gennari, C., 1996. Efficacy and safety of glucosamine sulfate in the treatment of gonarthritis. Clinica Therapeutics 147, 99–105.

Glaza, S.M., 2002. Acute oral toxicity study: glucosamine hydrochloride in rats. Covance 7350-100, 1–46.

Hanson, R.R., Smalley, L.R., Huff, G.K., White, S., Hammad, T.A., 1967. Oral treatment with a glucosamine-chondroitin sulfate compound for degenerative joint disease in horses: 25 cases. Equine Practice 19, 16–22.

Heart, E., Choi, W.S., Sung, C.K., 2000. Glucosamine-induced insulin resistance in 3T3-L1 adipocytes. American Journal of Physiology—Endocrinology Metabolism 278, E101–E112.

Houpt, J.B., McMillan, R., Wein, C., Paget-Dellio, S.D., 1999. Effect of glucosamine hydrochloride in the treatment of pain of osteoarthritis of the knee. Journal of Rheumatology 26, 2423–2430.

Hughes, R., Carr, A., 2002. A randomized, double-blind, placebo-controlled trial of glucosamine sulphate as an analgesic in osteoarthritis of the knee. Rheumatology 41, 279–284.

Institute of Medicine and National Research Council, 2004. Prototype monograph on glucosamine. In Dietary Supplements: a framework for evaluating safety. C-1–C-86.

Kashige, N., Kojima, M., Watanabe, K., 1991. Correlation between DNA breaking activity of amino sugars in and the amount of oxygen molecules generated in the aqueus solutions. Agricultural and Biological Chemistry 55, 1497–1505.

Kashige, N., Yamaguchi, T., Ohtakara, A., Mitsutomi, M., Brimacombe, J.S., Miake, F., Watanabe, K., 1994. Structure-activity relationships in the induction of single-strand breakage in plasmid pBR322 DNA by amino sugars and derivatives. Carbohydrate Research 257, 285–291.

Laine, L., 2001. Approaches to nonsteroidal antiinflammatory drug use in the high-risk patient. Gastroenterology 120, 594–606.

Leffler, C.T., Philippi, A.F., Leffler, S.G., Mosure, J.C., Kim, P.D., 1999. Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: a randomized, double-blind, placebo-controlled pilot study. Military Medicine 164, 85–91.

Manna, G., Banerjee, G., Gupta, S., 2004. Micronucleus test in peripheral erythrocytes of exotic fish, *oreochromis mossambica*. Nucleus 28, 176–179.

Marshall, S., Bacote, V., Traxinger, R.R., 1991. Discovery of a metabolic pathway mediating glucose-induced desensitization of the glucose transport system. Journal of Biological Chemistry 266, 4706–4712.

McAlindon, T.E., LaValley, M.P., Gulin, J.P., Felson, D.T., 2000. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. Journal of the American Medical Association 283, 1469–1475.

McNamara, T.E., Barr, S.C., Erb, H.N., 1996. Hematologic, hemostatic, and biochemical effects in dogs receiving an oral chondroprotective agent for thirty days. American Journal of Veterinary Research 57, 1390–1394.

Mecchi, M.S., 2003. *Salmonella–Escherichia coli*/mammallian-microsome reverse mutation assay with Cargill glucosamine hydrochloride. Covance 7178-124, 1–23.

Meininger, C.J., Kelly, K.A., Li, H., Haynes, T.E., Wu, G., 2000. Glucosamine inhibits inducible nitric oxide synthesis. Biochemical and Biophysical Research Communications 279, 234–239.

Milewski, S., 2002. Glucosamine-6-phosphate synthetase—the multi-facets enzyme. Biochimica et Biophysica Acta 1597, 173–192.

Monauni, T., Zenti, M.G., Cretti, A., Daniels, M.C., Targher, G., Caruso, B., Caputo, M., McClain, D., Del Prato, S., Giaccari, A.,

Muggeo, R.C., Bonora, E., Bonadonna, R.C., 2000. Effects of glucosamine infusion on insulin secretion and insulin action in humans. Diabetes 49, 926–935.

Mukherjee, D., Nissen, S.E., Topol, E.J., 2001. Risk of cardiovascular events associated with selective COX-2 inhibitors. Journal of the American Medical Association 286, 954–959.

Muller-Fabbender, H., Bach, G.L., Haase, W., Rovati, L.C., Setnikar, I., 1994. Glucosamine sulfate compared to ibuprofen in osteoarthritis of the knee. Osteoarthritis and Cartilage 2, 61–69.

Mund-Hoym, W.-D., 1980. Conservative treatment of vertebral osteoarthritis with glucosamine sulfate. Therapiewoche 30, 5922–5928.

Murad, H., Tabibian, M.P., 2001. The effect of an oral supplement containing glucosamine, amino acids, minerals, and antioxidants on cutaneous aging: a preliminary study. Journal of Dermatological Treatment 12, 47–51.

Nanjou, S., Fuii, S., Tanaka, K., Ueda, K., Komona, T., 1984. Induction of strand breakage in F174 RFI DNA by amino sugar derivatives. Agricultural and Biological Chemistry 48, 2865–2867.

Nelson, B.A., Robinson, K.A., Buse, M.G., 2000. High glucose and glucosamine induce insulin resistance via different mechanisms in 3T3-L1 adipocytes. Diabetes 49, 981–991.

Nguyen, P., Mohamed, S.E., Gardiner, D., Salinas, T., 2003. A randomized double-blind clinical trial of the effect of chondroitin sulfate and glucosamine hydrochloride on temporomandibular joint disorders: a pilot study. Journal of Craniomandibular Practice 19, 130–139.

Noack, W., Fischer, M., Forster, K.K., Rovati, L.C., Setnikar, I., 1994. Glucosamine sulfate in osteoarthritis of the knee. Osteoarthritis and Cartilage 2, 51–59.

Pavelka, K., Gatterova, J., Olejarova, M., Machacek, S., Giacovelli, G., Rovati, L.C., 2002. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind trial. Archives of Internal Medicine 162, 2113–2123.

Pouwels, M.J., Jacobs, J.R., Span, P.N., Lutterman, J.A., Smits, P., Tack, C.J., 2001. Short-term glucosamine infusion does not affect insulin sensitivity in humans. Journal of Clinical Endocrinology and Metabolism 86, 2099–2103.

Pujalte, J.M., Llavore, E.P., Ylescupidez, F.R., 1980. Double-blind clinical evaluation of oral glucosamine sulphate in the basic treatment of arthritis. Current Medical Research and Opinion 7, 110–114.

Qui, G.X., Gao, S.N., Giacovelli, G., Rovati, L., Setnikar, I., 1998. Efficacy and safety of glucosamine sulfate versus ibuprofen in patients with knee osteoarthritis. Drug Research 48, 469–474.

Reginster, J.Y., Deroisy, R., Rovati, L.C., Lee, R.L., Lejeune, E., Bruyere, O., Giacovelli, G., Henrotin, Y., Dacre, J.E., Gossett, C., 2001. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo-controlled clinical trial. Lancet 357, 251–256.

Reicheit, A., Forster, K.K., Fischer, M., Rovati, L.C., 1994. Efficacy and safety of intramuscular glucosamine sulfate in osteoporosis of the knee; a randomized, placebo-controlled, double-blind study. Arzneimittel-Forschung (Drug Research) 44, 75–80.

Richy, F., Bruyere, O., Ethgen, O., Cucherat, M., Henrotin, Y., Reginster, J.Y., 2003. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. Archives of Internal Medicine 163, 1514–1522.

Rindone, J.P., Hiller, D., Collacott, E., Nordhaugen, N., Arriola, G., 2000. Randomized, controlled trial of glucosamine for treating osteoarthritis of the knee. Western Journal of Medicine 72, 91–94.

Rovati, L.C., 1992. Clinical research in osteoarthritis: design and results of short-term and long-term trials with disease-modifying agents. International Journal of Tissue Reactions 14, 243–251.

Rovati, L.C., 1997. The clinical profile of glucosamine sulfate as a selective symptom modifying drug in osteoarthritis. current data and perspectives. Osteoarthritis and Cartilage 5, 72-abstract.

Sakai, K., Clemmons, D.R., 2003. Glucosamine induces resistance to insulin-like growth factor I (IGF-I) and insulin in Hep G2 cell cultures: biological significance of IGF-I/insulin hybrid receptors. Endocrinology 144, 2388–2395.

Scroggie, D.A., Albright, A., Harris, M.D., 2003. The effect of glucosamine-chondrotin supplementation on glycosylated hemoglobin levels in patients with type 2 diabetes mellitus: a placebo-controlled, double-blinded, randomized clinical trial. Archives of Internal Medicine 163, 1587–1590.

Senin, P., Makovec, F., Rovati, L., 1987. Rotta Research Laboratorium SPA, editor. Stable compounds of glucosamine sulphate. U.S. Patent 4,672,340.

Setnikar, I., Cereda, R., Pacini, M.A., Revel, L., 1991a. Antireactive properties of glucosamine sulfate. Arzneimittel-Forschung (Drug Research) 41, 157–161.

Setnikar, I., Giacchetti, C., Zanolo, G., 1984. Absorption, distribution and excretion of radioactivity after a single intravenous or oral administration of [14-C] glucosamine to the rat. Pharmacotherapeutica 3, 538–558.

Setnikar, I., Giacchetti, C., Zanolo, G., 1986. Pharmacokinetics of glucosamine in the dog and man. Arzneimittel-Forschung (Drug Research) 36, 729–735.

Setnikar, I., Pacini, M.A., Revel, L., 1991b. Antiarthritic effects of glucosamine sulfate studied in animal models. Arzneimittel-Forschung (Drug Research) 41, 542–545.

Setnikar, I., Palumbo, R., Canali, S., Zanolo, G., 1993. Pharmacokinetics of glucosamine in man. Arzneimittel-Forschung (Drug Research) 43, 1109–1113.

Setnikar, I., Rovati, L.C., 2001. Absorption, distribution, metabolism and excretion of glucosamine sulfate. a review. Arzneimittel-Forschung (Drug Research) 51, 699–725.

Shankland, W.E., 1998. The effects of glucosamine and chondroitin sulfate on osteoarthritis of the TMJ: a preliminary report of 50 patients. Journal of Craniomandibular Practice 16, 230–235.

Sigma Aldrich, 2001. Glucosamine hydrochloride and acetylglucosamine. Available from: <http://www.sigma-aldrich.com>.

Silverstein, F.E., Faich, G., Goldstein, J.L., Simon, L.S., Pincus, T., Whelton, A., Makuch, R., Eisen, G., Agrawal, N.M., Stenson, W.F., Burr, A.M., Zhao, W.W., Kent, J.D., Lefkowith, J.B., Verburg, K.M., Geis, G.S., 2000. Gastrointestinal toxicity with celecoxib vs nonsteroidal antiinflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized control trial. Celecoxib long-term arthritis safety study. Journal of the American Medical Association 284, 1247–1255.

Solomon, D.H., Schneeweiss, S., Glynn, R.J., Kiyota, Y., Levin, R., Mogun, H., Avorn, J., 2004. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation 109, 2068–2073.

Stender, S., Astrup, P., 1977. Glucosamine and experimental atherosclerosis. Increased wet weight and charged composition of cholesterol fatty acids in aorta of rabbits fed a cholesterol-enriched diet with added glucosamine. Atherosclerosis 26, 205–213.

Sugimura, T., Birnbaum, S.M., Winitz, M., Greenstein, J.P., 1959. Quantitative nutritional studies with water-soluble, chemically defined diets. IX. D-glucosamine-containing diets. Archives of Biochemistry and Biophysics 83, 521–527.

Takamiya, Y., Friedlander, R.M., Brem, H., Malick, A., Martuza, R.L., 1993. Inhibition of angiogenesis and growth of human nerve-sheath tumors by AGM-1470. Journal of Neurosurgery 78, 470–476.

Tannis, A.J., Barban, J., Conquer, J.A., 2004. Effect of glucosamine supplementation on fasting and non-fasting plasma glucose and serum insulin concentrations in healthy individuals. Osteoarthritis and Cartilage 12, 506–511.

Tapadinhas, M.J., Rivera, I.C., Bignamini, A.A., 1982. Oral glucosamine sulphate in the management of arthrosis: report of a multi-centre open investigation in Portugal. Pharmacotherapeutica 3, 157–168.

Thie, N.M.R., Prasad, N.G., Major, P.W., 2001. Evaluation of glucosamine sulfate compared to ibuprofen for the treatment of temporomandibular joint osteoarthritis: a randomized double blind controlled 3 month clinical trial. Journal of Rheumatology 28, 1347–1355.

Towheed, T.E., Anastassiaides, T.P., Shea, B., Houpt, J., Welch, V., Hochberg, M.C., 2004. Glucosamine therapy for treating osteoarthritis. Cochrane Database of Systematic Reviews, Issue 2. Art. No.: CD002946. DOI: 10.1002/14651858.CD002946.

Traxinger, R.R., Marshall, S., 1991. Coordinated regulation of glutamine:fructose-6-phosphate amidotransferase activity by insulin, glucose and glutamine. Role of hexosamine biosynthesis in enzyme regulation. Journal of Biological Chemistry 266, 10148–10154.

Uldry, M., Ibberson, M., Hosokawa, M., Thorens, B., 2002. GLUT2 is a high affinity glucosamine transporter. FEBS Letters 524, 199–203.

Vajranetra, P., 1984. Clinical trial of glucosamine compounds for osteoarthrosis of knee joints. Journal of the Medical Association of Thailand 67, 409–418.

Vas, A.L., 1982. Double-blind clinical evaluation of the relative efficacy of ibuprofen and glucosamine sulphate in the management of osteoarthrosis of the knee in out-patients. Current Medical Research and Opinion 8, 145–149.

Vosseller, K., Wells, L., Lane, M.D., Hart, G.W., 2002. Elevated nucleocytoplasmic glycosylation of O-GlcNAc results in insulin resistance associated with defects in Akt activation in 3T3-L1 adipocytes. Proceedings of the National Academy of Sciences of the United States of America 99, 5313–5318.

Wells, L., Vosseller, K., Hart, G.W., 2001. Glycosylation of nucleo-cytoplasmic proteins: signal transduction and O-GlcNAc. Science 291, 2376–2378.

Wells, L., Vosseller, K., Hart, G.W., 2003. A role for N-acetylglucosamine as a nutrient sensor and mediator of insulin resistance. Cell Molecular Life Science 60, 1–7.

Wolfe, M.M., Lichtenstein, D.R., Singh, G., 1999. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. New England Journal of Medicine 340, 1888–1899.

Wolosker, H., Kline, D., Bain, D., Blackshaw, S., Cameron, A.M., Fralich, T.J., Schnaar, R.L., Snyder, S.H., 1998. Molecularly cloned mammalian glucosamine-6-phosphate deaminase localizes to transporting epithelium and lacks oscillin activity. FASEB Journal 12, 91–99.

Wu, G., Haynes, T.E., Yan, W., Meininger, C.J., 2001. Presence of glutamine:fructose-6-phosphate amidotransferase for glucosamine-6-phosphate synthesis in endothelial cells: effects of hyperglycemia and glutamine. Diabetologia 44, 196–202.

Yamaguchi, T., Kashige, N., Matsumoto, S., Satoh, K., Yasuda, M., Watanabe, K., 1998. A carbon-centered radical as a reaction species in the DNA strand breakage by D-glucosamine. Biological Pharmacology Bulletin 21, 205–209.

Yanase, T., Tamura, M., Fujita, K., Kodama, S., Tanaka, K., 1993. Inhibitory effect of angiogenesis inhibitor TNP-470 on tumor growth and metastasis of human cell lines in vitro and in vivo. Cancer Research 53, 2566–2570.

Yu, J.G., Boies, S.M., Olefsky, J.M., 2003. The effect of oral glucosamine sulfate on insulin sensitivity in human subjects. Diabetes Care 26, 1941–1942.