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Glycobiology (2009) 19 (6): 564-567. doi: 10.1093/glycob/cwp014

First published online: March 2, 2009

Dietary glucosamine under question

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Abstract

Annual sales of glucosamine as a nutraceutical for affecting cartilage in treatment of osteoarthritis are close to a billion dollars, but recent clinical studies have currently raised severe criticism regarding its functional value. Additional doubts can be raised by the knowledge of the well-defined cellular steps in glucosamine formation and production of glycosaminoglycans such as chondroitin. Glucosamine is produced in an activated state from glucose by essentially all cells for incorporation into glycosaminoglycans and glycoproteins, and there have been no reports of any deficiencies in its production under any conditions. Nevertheless, many investigations of glucosamine, using cells or tissues, have claimed effects on cartilage and chondroitin sulfate. The significance of these studies is questionable since they have invariably been with concentrations that were 10- to 1000-fold higher than has been found in human serum or plasma after glucosamine ingestion. Experiments with cells or tissues using glucosamine in the low concentrations found after ingestion need to be examined before any conclusions are drawn concerning its direct action on cartilage and its potential for modifying osteoarthritis.

Key words chondroitin glucosamine glucose osteoarthritis

The Glyco-Forum articles (McClain 2008. *Glycobiology*. 18:651; Schnaar and Freeze 2008. *Glycobiology*. 18:652-657) on the "Glyconutrient Sham" published a few months ago brings to mind another glycosubstance group of considerable monetary size. Preparations of glucosamine chloride or glucosamine sulfate, usually together with chondroitin sulfate, have reached annual sales of nearly a billion dollars. In the United States, these substances are considered to be nutraceuticals, a Dietary Supplement as defined by the Dietary Supplement Health and Education Act passed by US Congress in 1994, and consequently do not have to demonstrate efficacy. However, they are prescription drugs in most European countries. The advertised usefulness for improving cartilage in treatment of osteoarthritis has been debated at great length, and two GAITS

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2008-2009-2010 have cast considerable doubt upon its value.

Our laboratory has focused its work on glycosaminoglycan metabolism for many years and particularly on the biosynthesis of chondroitin/dermatan sulfate (Silbert and Sugumaran 2002), sulfated glycosaminoglycan polymers of glucuronic/iduronic acid alternating with *N*-acetylgalactosamine. Glucosamine and galactosamine are produced entirely from circulating glucose by a series of intracellular reactions. The

glucose enters cells by 6-phosphorylation and is then changed to glucose 1-phosphate and converted to fructose 1-phosphate. It is then modified by an amino transferase to form glucosamine 1-phosphate. This is then *N*-acetylated, followed by reaction with UTP to form UDP-*N*-acetylglucosamine which serves as the donor of the glucosamine component of hyaluronan, heparin, and heparin sulfate as well as glycoproteins. The UDP-*N*-acetylglucosamine can also be epimerized to form UDP-*N*-acetylgalactosamine which serves as the donor of the galactosamine component of chondroitin/dermatan sulfate as well as glycoproteins. When glucosamine is provided to tissues or cultured cells for experimental purposes, it can enter cells by 6-phosphorylation (although much less efficiently than glucose) with conversion to glucosamine 1-phosphate by the same enzymes that produce glucose 1-phosphate followed by acetylation to form the same *N*-acetylglucosamine 1-phosphate substrate for the formation of UDP-*N*-acetylglucosamine. This alternate pathway does not occur in vivo since essentially no free glucosamine appears in animal tissues.

For experimental purposes, we and many other investigators have examined the in vitro biosynthesis of glycosaminoglycans and glycoproteins in tissue or cell culture by incubations with ^3H - or ^{14}C -labeled glucosamine. This is a highly useful method, and our laboratory has utilized it extensively for investigations of the cellular biosynthesis of chondroitin sulfate, dermatan sulfate, heparin, and heparan sulfate. However, quantification of the amount of glycosaminoglycan synthesized would be unknown since an indeterminate proportion of the hexosamine incorporated into glycosaminoglycans would be from nonlabeled glucosamine produced from glucose by the main pathway.

In order to quantify the synthesis, we developed the technique of incubating cells with [^3H]glucosamine together with [^{35}S]sulfate and then determined the specific activities of the [^3H , ^{35}S]glycosaminoglycans that were formed (Kleinman et al. 1975; Humphries et al. 1989; Silbert et al. 1989). Since most cells are incapable of forming sulfate, the [^{35}S]sulfate would not be diluted, and the specific activity of [^{35}S]sulfate in the products would be the same as the specific activity of the [^{35}S]sulfate in the incubation media. Using production of chondroitin sulfate that most cells make, we then utilized a chondroitinase to degrade the ^3H , ^{35}S product to form sulfated disaccharides containing equal amounts of galactosamine and sulfate. Since the amount of ^{35}S reflected total production while the amount of ^3H reflected only the amount of galactosamine derived from [^3H]glucosamine in the media, the ratio of the ^3H to ^{35}S in the product compared to the ratio in the media provided a direct calculation of the percentage of galactosamine derived from [^3H]glucosamine in the media compared to the percentage of galactosamine derived from glucose.

We generally used low concentrations of [^3H]glucosamine with high specific activity in order to maximize the amounts of radioactivity in the glycosaminoglycan products. Under these conditions, we found that the radioactive glucosamine was diluted many fold by glucosamine formed from glucose. For example, when 0.002 mM [^3H]glucosamine was incubated with human skin fibroblasts from six individuals, dilution by glucosamine derived from glucose was 160- to 635-fold (Silbert et al. 1989). Because of this dilution by glucosamine formed from glucose, we questioned the likelihood that stimulation of cartilage chondroitin sulfate synthesis by glucosamine could be a factor in treating osteoarthritis unless significant levels of glucosamine could be provided to the cells. Thus, to determine the potential effect of glucosamine levels on cartilage, we incubated cultures of mouse chondrocytes (Mroz and Silbert 2003) and human chondrocytes (Mroz and Silbert 2004) for 5 h with varying concentrations of [^3H]glucosamine in the presence of a fixed

concentration of [³⁵S]sulfate and physiological level of glucose (5.5 mM). With human chondrocytes, we found that only 0.3% of the chondroitin galactosamine was obtained from 0.0017 mM [³H]glucosamine, 1.6% from 0.01 mM, and 9% from 0.1 mM. Similar results were found with the mouse chondrocytes. There was no stimulation of total chondroitin synthesis as measured by incorporation of [³⁵S]sulfate at these levels. Higher percentages derived from [³H]glucosamine could be achieved with 0.3 mM [³H]glucosamine (15%) and 1.0 mM (30%), while total synthesis as measured by incorporation of [³⁵S]sulfate dropped at these higher [³H]glucosamine levels. These results suggested that oral glucosamine might have no direct effect in stimulating chondroitin formation and could even decrease formation at higher glucosamine levels.

It was clear that actual measurement of glucosamine serum levels after oral ingestion in humans would be fundamental to gaining any perspective concerning the potential for glucosamine stimulation of chondroitin formation. It had been reported (Setnikar et al. 1986) that no glucosamine was measurable in human plasma after ingestion of four times the usual 1500 mg of glucosamine chloride or sulfate when measured by a technique that required 0.55 mM for any detection. There was no other information in the literature relating to human blood glucosamine levels. After trying several techniques, we found that we could measure glucosamine down to 0.0005 mM by use of high-performance liquid ion-exchange chromatography with a pulsed amperometric detection method using a Metrohm–Peak 817 Bioscan apparatus (Biggee et al. 2006, 2007a). Eighteen subjects were recruited and given 1500 mg of glucosamine sulfate after an overnight fast. Serum glucosamine levels of blood drawn from all subjects before ingestion were below the 0.0005 mM sensitivity of the method. Serum levels of blood drawn every 15 to 30 min for 3 h after ingestion demonstrated a range in individual subjects with maximums from 0.002 to 0.012 mM at 2 to 3 h. Overall mean maximum for the 18 participants was 0.0048 mM. Thus, for a short period of time, the serum levels reached a concentration that provided less than 0.3% of the glucosamine for synthesis of chondroitin sulfate after a 5 h culture of chondrocytes. Similar glucosamine levels were found by investigators (Persiani et al. 2005) from Rotta Research Laboratorium (commercial producers of glucosamine sulfate for osteoarthritis) using a different methodology and published at about the same time ours was published online. They claimed that a steady-state mean of about 0.007 mM was reached at 3 h which was contrary to our results that demonstrated a decline to minimal levels by 8 h with no development of a steady state.

Although we found no glucosamine stimulation of chondroitin synthesis by cultured chondrocytes at any concentration, there have been a number of reports describing stimulation of cartilage or chondroitin synthesis in cartilage explants and/or chondrocytes (Bassleer et al. 1998; Adebawale et al. 2002; Aghazadeh–Habashi et al. 2002; Derfoul et al. 2007; Varghese et al. 2007), but all with long-term 0.1–10 mM concentrations of glucosamine, as much as 10- to 1000-fold greater than the highest serum concentrations we have found. It is of note that another study (Terry et al. 2007) described concentration-related reductions rather than increases in chondroitin synthesis in the presence of glucosamine as low as 0.1 mM. Other reports have indicated some effects on chondroitin proteoglycan core protein aggrecan formation by cultured chondrocytes at levels 10- to 20-fold higher (Dodge and Jimenez 2003), as well as inhibition of aggrecan degradation at levels 200- to 500-fold higher (Sandy et al. 1998; Ilic et al. 2003) or reduction in cartilage degradation at 200- to 2000-fold higher (Fenton et al. 2000). Reduction in degradative enzymes have also been reported but with glucosamine concentrations that were 10- to 50-fold higher (Piperno et al. 2000) as well as anabolic and catabolic effects on aggrecan (Uitterlinden et al. 2006) but only with

1000-fold higher glucosamine. There are also a number of publications relating to the effects of glucosamine on IL1 β -mediated or other substance-mediated modifications of chondrocyte and proteoglycan synthesis or degradation (Gouze et al. 2001, 2002; Dodge and Jimenez 2003; Largo et al. 2003). These experiments generally utilized glucosamine concentrations that were 1000-fold or more higher, although there are reports of effects on chondrocytes using only a 3- to -6-fold increment (Chan et al. 2005, 2007), but with incubations as long as 2 days to 2 weeks. Glucosamine at 20- to 200-fold higher concentration has been reported to inhibit neutrophil function in osteoarthritis (Hua et al. 2002), and 500- to 2000-fold higher concentrations have been reported to decrease the activation of T lymphocytes with claims of immunosuppression as a role for glucosamine (Ma et al. 2002). In contrast to these positive reports at exceedingly high concentrations, 0.01-0.1 mM glucosamine concentrations (0- to 10-fold) were reported to have no effect on aggrecan or chondroitin synthesis (Qu et al. 2006).

We have concluded that insignificant trace amounts of glucosamine enter human serum after ingestion of a standard oral dose of glucosamine sulfate or glucosamine chloride (1500 mg), far below any amount that might contribute directly to chondroitin synthesis. Moreover, this level is limited to a few hours after ingestion, with no establishment of any substantial lasting concentration. It is far below most of the concentrations used for in vitro cell or tissue culture incubations by others, usually for days or weeks, in proposing mechanisms to protect chondrocytes, inhibit chondroitin degradation, diminish inflammation, or provide immunosuppression in articular cartilage mechanisms. All of these presuppose that significant amounts get into cartilage after oral ingestion and neglect the evident limitation of blood levels of glucosamine by a first passage from the portal system through the liver before reaching the peripheral circulation. Until consistent actions on cartilage can be demonstrated at the low concentration and limiting time periods that we found, claims of a meaningful direct effect on cartilage or chondrocytes are questionable. Alternatively, the high concentrations of liver glucosamine could cause changes or production of liver substances that might affect cartilage. However, no information of this sort has been reported.

In general, it has been assumed that there are no deleterious side effects in use of the standard amounts of glucosamine. However, there has been work unrelated to cartilage metabolism suggesting that glucosamine might affect insulin resistance and glucose transport (Marshall et al. 1991; Hebert et al. 1996; McClain and Crook 1996; Stumpf and Lin 2006; Pham et al. 2007). For this reason, we examined the effects of glucosamine on glucose and insulin levels in our subjects when given together with a glucose tolerance test (Biggee et al. 2007b). We found slight but not significant mean glucose elevations in 13 nondiabetic subjects when given glucosamine. However, there were statistically significant glucose elevations with glucosamine ingestion by three subjects who were found by the glucose tolerance test to have previously undiagnosed diabetes. This is the first time that results of this sort have been found with diabetics that were not under treatment and warrant further investigation.

Funding

Medical Research Service of the Department of Veterans Affairs, Arthritis Foundation, Tufts University General Clinical Research Center NIH grant MO1-RR00054.

Conflict of interest statement

None declared.

Published by Oxford University Press 2009.

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