# The Effect of Glucosamine on Serum HDL Cholesterol and Apolipoprotein AI Levels in People With Diabetes

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**OBJECTIVE** — Dietary and nutritional supplements are modulators of HDL cholesterol levels and production of apolipoprotein (apo) AI. Previously, in vitro treatment of hepatocyte cell lines with glucosamine increased apoAI production by stabilization of apoAI mRNA. The hypothesis is that the neutraceutical glucosamine, when given in conventional doses (1,500 mg/day) may increase apoAI and HDL cholesterol levels in subjects with diabetes and low HDL cholesterol.

**RESEARCH DESIGN AND METHODS** — Twelve subjects (three men and nine women) with type 1 ($n = 2$) and type 2 ($n = 10$) diabetes, aged 55 ± 12 years (mean ± SD), who had low HDL cholesterol (1.03 ± 0.20 mmol/l), were randomly assigned to a double-blind, placebo-controlled, cross-over trial of 500 mg glucosamine or placebo orally three times daily for 2 weeks, followed by a 4-week washout phase and a 2-week cross-over to the alternate therapy.

**RESULTS** — Fasting serum glucose, fructosamine, and total cholesterol remained stable during the drug and placebo phases. Glucosamine had no significant effect after therapy on serum levels of HDL cholesterol (from baseline of 1.02 ± 0.15 to 1.05 ± 0.16 mmol/l compared with placebo from 1.04 ± 0.21 to 1.06 ± 0.16 mmol/l) nor in changes in apoAI levels (from baseline of 147 ± 15 to 140 ± 126 mg/dl with glucosamine and from 146 ± 25 to 142 ± 17 mg/dl with placebo).

**CONCLUSIONS** — These observations suggest that glucosamine at commonly consumed doses does not have significant effects on glycemic control, lipid profile, or levels of apoAI in diabetic subjects after 2 weeks of supplementation.

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It is generally accepted that the mechanism of the increased risk of cardiovascular disease in diabetes is multifactorial (1). One such factor is probably the reduced serum levels of HDL in obese type 2 diabetic individuals (1,2). Dietary composition and nutritional supplements are important modulators of the HDL cholesterol level and the production of its main apolipoprotein (apo), namely, AI (3). Glucosamine, a popular nutritional supplement for treating arthritis, has been shown to alter apoAI production in hepatocyte cultures (4).

Endogenous glucosamine is synthesized by the amidation of glucose-6-phosphate via the hexosamine biosynthetic pathway (5). Approximately 5% of glucose-6-phosphate is metabolized to *N*-acetylglucosamine by glutamine: fructose-6-phosphate amidotransferase. In addition, the extracellular glucosamine is transported into tissues and is subsequently phosphorylated to enter the hexosamine biosynthetic pathway. This pathway has been implicated in insulin resistance that may contribute to diabetes and cardiovascular diseases (5).

Commercially available products containing glucosamine are used extensively as neutraceuticals in the treatment of arthritis and have been shown in large clinical trials to be safe in conventional doses (1,500 mg/day) (6,7). Parenteral administration of high doses of glucosamine (i.e., 5–30 $\mu mol \cdot kg^{-1} \cdot min^{-1}$) may cause diabetes in experimental animals (8). Studies in healthy human control subjects who received a peripheral infusion of low-dose glucosamine (1.6 $\mu mol \cdot kg^{-1} \cdot min^{-1}$, steady-state plasma levels of 0.57 mmol/l) showed no change in parameters of glucose homeostasis. High-dose, continuous infusion of glucosamine (5 $\mu mol \cdot kg^{-1} \cdot min^{-1}$, steady-state plasma levels of 1.15 mmol/l) was associated with minimal abnormalities in insulin secretion, glucose tolerance, or insulin-mediated glucose metabolism (8). Furthermore, clinical trials in subjects with type 2 diabetic subjects have shown that glycemic control does not deteriorate after treatment with 1,500 mg glucosamine/1,200 mg chondroitin per day over 90 days' duration (9).

We have previously reported that treatment of hepatocyte cell lines in culture with glucosamine increases apoAI production as a result of stabilization of apoAI mRNA (4). It is not known whether this observation is clinically relevant and whether glucosamine supplementation in diabetic subjects, who tend to have low apoAI levels, would ameliorate the hypoalphalipoproteinemic state. Improvements in apoAI and HDL cholesterol levels by glucosamine could potentially reduce the cardiovascular risk in diabetes. Therefore, the present study was performed to test the hypothesis that glucosamine supplementation, when given in currently acceptable doses, may increase apoAI and HDL cholesterol levels in subjects with diabetes and low HDL cholesterol.

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**Abbreviations:** Apo, apolipoprotein.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

**Table 1—*Demographics and baseline laboratory findings of study participants at screening visit***

| Parameters | Value |
|---|---|
| Sex (male/female) | 3/9 |
| Diabetes type (1/2) | 2/10 |
| Age (years) | 55 ± 12 |
| Height (m) | 1.75 ± 0.14 |
| Weight (kg) | 114.9 ± 42.5 |
| BMI (kg/m$^2$) | 36.7 ± 9.9 |
| Hypolipemic drugs (doses) | |
| Atorvastatin (10 mg/20 mg/80 mg) | 1/1/1 |
| Lovastatin (20 mg/40 mg) | 1/1 |
| Pravastatin (40 mg) | 2 |
| Nicotinic acid (2,000 mg) | 1 |
| Ezetimibe (10 mg) | 1 |
| Ezetimibe (10 mg) + rosuvastatin (10 mg) | 1 |
| None | 2 |
| A1C (%) | 7.9 ± 1.4 |
| Fructosamine (μmol/l) | 289 ± 71 |
| Fasting glucose (mmol/l) | 9.12 ± 4.04 |
| Total cholesterol (mmol/l) | 4.16 ± 0.75 |
| HDL cholesterol (mmol/l) | 1.03 ± 0.20 |
| LDL cholesterol (mmol/l) | 2.24 ± 0.68 |
| Triglycerides (mmol/l) | 2.65 ± 1.44 |
| ApoA1 (mg/dl) | 146 ± 19 |
| ApoB (mg/dl) | 95 ± 18 |

Data are *n* or means ± SD.

## RESEARCH DESIGN AND METHODS

— Subjects with either type 1 or type 2 diabetes were recruited from the endocrinology clinics of Saint Louis University. Inclusion criteria were HDL cholesterol ≤1.29 mmol/l and at least one of the following: triglycerides ≥2.30 mmol/l, abdominal obesity (waist circumference >102 cm in men or >88 cm in women), or hypertension (blood pressure >130/85 mmHg before treatment). They were randomly assigned to a double-blind, placebo-controlled, cross-over trial of 500 mg glucosamine orally three times a day or matching placebo for 2 weeks, followed by a 4 week washout phase and then a 2-week cross-over to the alternate therapy of placebo or glucosamine.

All subjects had stable A1C and were not allowed to have had any new class of antiglycemic medications within the previous 2 months before enrollment. Subjects who were already taking lipid-modifying agents, such as statins, fibrates, niacin, ezetimibe, binding resins, glitazones, fish oil, estrogen, or selective estrogen receptor modulators, for at least the preceding 2 months continued without change in the dose of medication. Subjects were excluded if they had any recent myocardial infarction or revascularization procedure (within 6 weeks), renal disease (serum creatinine >177 μmol/l), recent surgery (within 6 weeks), weight loss of >5% of body weight within the preceding 3 months, liver disease (abnormal liver enzymes or liver function tests), or chronic hepatitis or were pregnant.

All subjects signed a consent form approved by the Institutional Review Board of Saint Louis University. They were randomly assigned by computer-generated random number allocation to initial treatment with glucosamine or matching placebo. Independent analysis of random pills were determined to be >99.5% pure by chemical analysis of glucosamine content by high-performance liquid chromatography (10).

Laboratory measurements were performed in the clinical laboratories of Quest Diagnostics (St. Louis, MO) using standard laboratory ranges of glucose, cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, A1C, fructosamine (reference range 190–270 μmol/l), apoAI (reference range for males 94–176 mg/dl and females 101–198 mg/dl) and apoB (reference range for males 52–109 mg/dl and females 49–103 mg/dl).

**Statistical analysis.** Changes in lipid levels and lipoprotein levels were analyzed by paired parametric testing with ANOVA of repeated measures. The efficacy of glucosamine in increasing hepatic apoAI production in cell culture studies was used to calculate the number of subjects needed to demonstrate a clinical effect. In these cell culture studies, glucosamine treatment of cells at the lowest dose tested (0.03 mmol/l) was associated with an 80% increase in apoAI levels in the culture media (4). It was estimated that to demonstrate a 10% improvement in apoAI levels with glucosamine treatment, 12 subjects would have a power of >80% for an $\alpha = 0.05$ by two-tailed paired testing.

Statistical procedures were performed with the statistical package Statistica for Windows (version 7; Statsoft, Tulsa, OK). Significance was defined as $P < 0.05$ by two-tailed testing.

## RESULTS AND CONCLUSIONS

— Twelve subjects with type 1 ($n = 2$) and type 2 ($n = 10$) diabetes were enrolled. The demographics of the study population are summarized in Table 1. Table 2 summarizes the glycemic and lipid profiles of the subjects throughout the study. Treatment with glucosamine, 500 mg three times a day for 2 weeks, did not alter the glycemic control parameters such as fasting glucose or fructosamine level and did not alter the serum lipid and lipoprotein levels.

The lack of a significant effect on glycemic parameters is consistent with previously published studies on the effect of glucosamine in both diabetic and nondiabetic individuals (9,11). Of particular interest in this study was the lack of a change in HDL cholesterol or apoAI levels after glucosamine treatment for 2 weeks. This outcome was contrary to our expectations based on our previous studies showing a significant effect of glucosamine on apoAI production in hepatocytes (4).

Several potential variables may explain the discrepancy between the in vivo effects of glucosamine and the effects observed in cell cultures. Interference of glucosamine with the assays reported is unlikely and has not been previously observed (8,9,11). The half-life of apoAI has been estimated to be 15–54 h (12). In individuals with diabetes and hypertriglyceridemia, the fractional catabolic rate of HDL and apoAI is increased (13). Thus, given the known kinetics of apoAI and HDL cholesterol, 2 weeks of treatment is

**Table 2—*Serum concentrations of glucose, fructosamine, lipid, and lipoproteins before and after 2 weeks of treatment with glucosamine (500 mg) or placebo orally three times a day***

| | Glucosamine | | Placebo | |
|---|---|---|---|---|
| Parameter | Before | After | Before | After |
| Glucose (mmol/l) | 9.5 ± 5.4 | 10.3 ± 4.9 | 9.5 ± 4.2 | 10.5 ± 6.2 |
| Cholesterol (mmol/l) | 4.16 ± 0.63 | 4.14 ± 0.77 | 4.20 ± 0.76 | 4.19 ± 0.84 |
| HDL cholesterol (mmol/l) | 1.02 ± 0.15 | 1.05 ± 0.16 | 1.04 ± 0.21 | 1.06 ± 0.16 |
| LDL cholesterol (mmol/l) | 2.19 ± 0.59 | 2.26 ± 0.58 | 2.20 ± 0.65 | 2.12 ± 0.63 |
| Triglycerides (mmol/l) | 2.81 ± 1.49 | 2.64 ± 1.97 | 2.86 ± 1.61 | 3.02 ± 2.01 |
| Fructosamine (μmol/l) | 309 ± 104 | 330 ± 139 | 298 ± 74 | 327 ± 97 |
| ApoA1 (mg/dl) | 147 ± 15 | 140 ± 16 | 146 ± 25 | 142 ± 17 |
| ApoB (mg/dl) | 91 ± 22 | 89 ± 17 | 91 ± 16 | 95 ± 27 |

Data are means ± SD.



sufficient to demonstrate a meaningful effect on steady-state levels of HDL cholesterol and apoAI.

The dose of glucosamine, however, may have been insufficient to effect a change. The choice of the dose was based on the dose that is commonly prescribed and on precautionary considerations that higher doses of glucosamine may have adverse metabolic effects (11). A single oral dose of 500 mg glucosamine results in a peak concentration of 2–5 μmol/l and is eliminated with a mean apparent plasma elimination half-life of 148 min (11). Given such elimination kinetics, the plasma glucosamine levels would not reach a steady state when glucosamine supplements are taken on a three-times-a-day schedule.

If the peak concentration achievable after a 500-mg dose of oral glucosamine is 5 μmol/l and if we assume that hepatic first-pass metabolism accounts for 25% bioavailability of glucosamine (11), it can be assumed that the liver is exposed to concentrations of glucosamine in the range of 20 μmol/l. This amount is somewhat lower than the lowest concentration of glucosamine (30 μmol/l) used in cell culture studies (4). Thus, the dwell time in plasma may be short and the concentration not high enough for the intended effect. It is possible that higher or more frequent dosing may have an effect on apoAI metabolism, but there is insufficient safety data available to make these dose adjustments.

Another potential confounding factor is the variability of the active ingredient content of glucosamine pills (10). Therefore, we measured the active ingredient in a random samples of the pills used in the study to document the reliability of the commercial product.

The sample size may have limited the capacity of this study to detect a significant effect of glucosamine on apoAI levels. The magnitude of the increase in apoAI production after glucosamine treatment of hepatocytes in cultures was highly significant (4). Glucosamine was used at doses of 0.03, 0.1, 0.3, 1.0, and 3.0 mmol/l. The changes in apoAI were significant even at 0.03 mmol/l (763 vs. baseline values of 423 arbitrary integrator units), and at 1.0 mmol/l there was a 5.5-fold increase in apoAI protein and a 2.4-fold increase in apoAI mRNA. The current study was designed to document a 10% change in apoAI. Twelve subjects would have been sufficient to provide a power of >80% at an $\alpha = 0.05$ to demonstrate a 10% improvement in apoAI levels with glucosamine treatment by two-tailed testing. It is possible that given the limited number of subjects studied, a more modest increase in apoAI levels may have been missed.

It is also possible that given the multiplicity of factors that suppress apoAI production in diabetes (2), the effect of glucosamine will not be demonstrable in this population. It is noteworthy that a recent study in nondiabetic lean or obese subjects could not show a significant change in HDL cholesterol levels after 6 weeks of treatment with 1,500 mg glucosamine daily (11).

A recently published randomized, placebo-controlled study examined whether glucosamine has an antirheumatic effect in 51 patients with rheumatoid arthritis (14). Glucosamine hydrochloride at a daily dose of 1,500 mg and placebo were administered for 12 weeks along with conventional medication. Although significant improvement was not found in objective measures of severity of disease, pain was significantly reduced in the glucosamine group. Because glucosamine has been used in the treatment of osteoarthritis (6,7) and rheumatoid arthritis (14), it would therefore be useful to know the effect of this treatment on the plasma lipid profile. The mechanism of action of glucosamine in its antiarthritic effect is largely unknown but seems to involve an anti-inflammatory effect (15). This implies an effect on circulating inflammation mediators, some of which, notably tumor necrosis factor-α and interleukin-1β are known to downregulate apoAI production and reduce HDL cholesterol levels (16,17). Thus, it is possible that the potential salutary effects of glucosamine on HDL cholesterol may be more pronounced in those individuals in a chronic inflammatory state such as arthritis, compared with nonarthritic patients with diabetes in whom the degree of chronic inflammation may be less.

Overall these observations suggest that glucosamine at doses commonly consumed by the public does not have significant effects on glycemic control or lipid profiles of subjects with diabetes after 2 weeks of supplementation. The effects of glucosamine previously shown in hepatocyte cultures are not demonstrable clinically in subjects with diabetes when glucosamine is consumed in commonly used amounts.

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