The Effect of Glucosamine-Chondroitin Supplementation on Glycosylated Hemoglobin Levels in Patients With Type 2 Diabetes Mellitus

A Placebo-Controlled, Double-blinded, Randomized Clinical Trial

Daren A. Scroggie, MD; Allison Albright, MD; Mark D. Harris, MD

Background: With increasing use of glucosamine-containing supplements for the treatment of osteoarthritis, there is increasing concern in the medical community about possible toxic effects. The present study was undertaken to determine whether glucosamine supplementation altered hemoglobin A1c concentrations in patients with well-controlled diabetes mellitus.

Objective: To evaluate possible effects of glucosamine supplementation on glycemic control in a selected population of patients with type 2 diabetes mellitus.

Design: Placebo-controlled, double-blinded, randomized clinical trial.

Setting: Outpatient, diabetes monitoring clinic.

Patients: Patients were typically elderly patients, evenly divided between men and women. Most of the patients were being treated with 1 or 2 drugs for glycemic control.

Intervention: In daily doses for 90 days, patients received either placebo or a combination of 1500 mg of glucosamine hydrochloride with 1200 mg of chondroitin sulfate (Cosamin DS; Nutramax Laboratories Inc, Edgewood, Md).

Main Outcome Measure: Hemoglobin A1c levels before and after 90 days of therapy.

Results: There were 4 withdrawals from the glucosamine-treated group. Three were related to comorbidities (myocardial infarction, congestive heart failure, and atrial fibrillation) and 1 to a possible adverse reaction (excessive flatus). No other patient reported any adverse effects of glucosamine therapy, and no patient had any change in their diabetes management. Mean hemoglobin A1c concentrations were not significantly different between groups prior to glucosamine therapy. Posttreatment hemoglobin A1c concentrations were not significantly different between groups, nor were there any significant differences within groups before and after treatment.

Conclusion: This study demonstrates that oral glucosamine supplementation does not result in clinically significant alterations in glucose metabolism in patients with type 2 diabetes mellitus.

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and if this is true, there is a theoretical risk of altering the glucose metabolism in humans. The *Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements* carries a precaution about the use of glucosamine for patients with diabetes. Therefore, if it could be shown that glucosamine, in doses and formulations available to patients over the counter, did not affect glycemic control, it might be used as an alternative therapy. This study was designed as a placebo-controlled, double-blinded, randomized clinical trial to determine the clinical effect of glucosamine supplementation on serum glucose levels in patients with type 2 diabetes mellitus.

## METHODS

### STUDY DESIGN

The study was a 90-day, placebo-controlled, double-blinded, randomized clinical trial performed at a single medical center in the southwestern United States. The study followed the 1975 Declaration of Helsinki as revised in 1983, with institutional review board approval and written and oral informed consent obtained from all patients. Personnel not otherwise involved in the study assigned patients to either glucosamine or placebo at the central pharmacy in a 2:1 block randomization scheme. Placebo and glucosamine capsules were identical in appearance. Patients and investigators were blinded to the assigned treatment arm.

### PATIENTS

Patients were selected from the Wilford Hall Medical Center Diabetes Care Clinic, Lackland Air Force Base, Lackland, Tex, a multidisciplinary clinic treating mainly elderly patients with stable type 2 diabetes mellitus. The patients were identified by their staff endocrinologists after completing a routine follow-up visit and were asked if they wished to participate in the study. Those who expressed interest were given an information pamphlet on Cosamin DS (Nutramax Laboratories Inc, Edgewood, Md) and asked about their current medications.

Patients included in the study were required to have a confirmed diagnosis of type 2 diabetes mellitus, be undergoing treatment with a stable dose of oral antihyperglycemic medications or be under strict diet control, and have a stable hemoglobin A1c (HbA1c) level (varied by less than 0.2%) for at least 2 consecutive measurements separated by at least 90 days. Patients taking insulin or those with unstable blood glucose levels (eg, recently diagnosed patients or those taking either a new medication or new dose of current medicine) were excluded. In addition, patients taking glucocorticoids were excluded.

### TREATMENT

For the duration of the trial, patients took 2 capsules in the morning and 1 in the evening. The treatment capsules were Cosamin DS, containing 500 mg of glucosamine hydrochloride (FCHG49; Nutramax Laboratories Inc), 400 mg of low-molecular-weight sodium chondroitin sulfate (TRH122; Nutramax Laboratories Inc), 5 mg of manganese, and 66 mg of ascorbic acid. This formulation has proven to be bioavailable and to meet all label claims of content in published research. Placebo capsules contained cellulose and were identical in size and shape to the treatment capsules. Prior to study approval, samples were tested for purity using high-performance liquid chromatography and were found to contain the stated amounts of glucosamine and chondroitin. Patients monitored daily finger-stick glucose values and were instructed to return to the clinic for any persistent elevations over baseline values. They were instructed to continue baseline diabetes medications and report any changes to clinic personnel. Patients returned their daily blood sugar log and completed an exit questionnaire detailing any changes in medications, hospitalizations, or illnesses that occurred during their trial participation.

### DATA ANALYSIS

All patients completed an entry questionnaire and had baseline serum drawn for analysis of HbA1c levels. Hemoglobin A1c was measured by ion-exchange high-performance liquid chromatography (A1c 2.2 Plus Glycohemoglobin Analyzer; Tosoh Medics, San Francisco, Calif). The machine was calibrated daily and certified with the National Glycohemoglobin Standardization Program.

### RESULTS

A total of 113 patients were eligible for study participation, 74 of whom elected not to participate. Reasons given by patients for not participating included aversion to being “study patient,” desire to take as few medications as possible, distrust of “herbal medicines,” and desire to continue current use of glucosamine product. A total of 39 patients elected to participate in the study. One of these patients gave consent but never picked up study medication (was not randomized). Of the remaining 38 patients in the study, 26 were randomized to treatment and 12 to placebo. Four patients withdrew from the study, all of whom were in the treatment arm. Reasons for withdrawal were believed to be unrelated to glucosamine or worsening glycemic control in 3 of the 4 (myocardial infarction, congestive heart failure, and worsening of chronic atrial fibrillation). The remaining patient withdrew early owing to excessive flatus (a possible adverse effect of glucosamine). These patients were among the oldest patients in the study, with a mean age of 79.3 years, and this may account for their comorbidities. This left 22 patients in the glucosamine group to compare with 12 patients in the placebo group.

At baseline, the groups were similar demographically. Glycemic control, as reflected by HbA1c levels, was equivalent between the two. Patients in the placebo group appeared to have somewhat milder disease, with fewer patients requiring therapy with antihyperglycemic medications.

The HbA1c mean values changed very little in both groups during the study. In the glucosamine arm, the
mean HbA1c value increased from 6.45% to 6.50%. This change was not significant. In the placebo arm, the HbA1c value decreased from 6.25% to 6.09%, a change of 0.16 percentage points which was also not significant. The analysis of variance also showed that there were no significant differences between the groups (P = .20). Post hoc analysis revealed that the sample sizes of 22 in the treatment arm and 12 in the placebo arm yielded a power of 80% to detect a large difference (>0.3%) between the groups and a power of 80% to detect a change of 0.15 from before to after treatment in the glucosamine-treated group.

There were no changes in medical therapy in either group during the study period. With the exception of the hospitalized patients, there were no increased physician visits in either group.

### COMMENT

While the pathogenesis of diabetes has not been completely defined, the current understanding is that most type 2 diabetes mellitus develops when β-cell production of insulin can no longer overcome the body’s resistance to the effects of insulin. Instability in the maintenance of glucose homeostasis is the hallmark of diabetes. Measurement of HbA1c levels is a well-accepted and widely used indicator of the hyperglycemic control among patients with diabetes. In the present study, we report the first human placebo-controlled, double-blinded, randomized clinical trial that evaluates the potential adverse effect of a specific grade of glucosamine hydrochloride on the control of blood glucose among patients with type 2 diabetes mellitus. Hemoglobin A1c was selected as the indicator of blood glucose because it is the most common measure of glycemic control in clinical trials and in the management of diabetes.

There are 2 possible mechanisms through which glucosamine could affect blood glucose: by acting as a source of glucose or by interfering with the regulation of blood glucose. It is unlikely that glucosamine would be converted directly to glucose because the enzymatic pathway is irreversible in humans. If it were possible to convert the entire dose of glucosamine to glucose, the total amount of glucose would only be 1500 mg/d.

The second possible mechanism involves the role of glucosamine and the hexosamine biosynthesis pathway in the regulation of glucose transport. Endogenous glucosamine is synthesized from fructose-6-phosphate and glucose by the enzyme glutamine:fructose-6-phosphate amidotransferase (GFAT) in the hexosamine pathway. This pathway represents an alternative metabolic destiny for glucose. Overexpression of GFAT results in high levels of glucosamine and insulin resistance in animal models. In normal cellular situations, the glucose is shunted into the hexosamine pathway when intracellular energy requirements have been met. Experimental models suggest that the shift to hexosamine production acts as a signal that intracellular glucose levels are sufficient and that further influx of glucose is not needed. This results in decreased uptake of extracellular glucose via down-regulation of glucose transport receptors. This insulin resistance can occur even in the face of hyperglycemia and insulin stimulation.

In theory, exogenous glucosamine could bypass the normal metabolic regulations of GFAT and signal that the cell has adequate glucose stores. Glucose transport would be curtailed, which could then lead to hyperglycemia and insulin resistance.

Several experimental studies have been undertaken to evaluate the effects of exogenous glucosamine on regulation of glucose. In these studies, large amounts of glucosamine were intravenously infused into animals. Under these conditions, glucosamine tended to decrease insulin secretion and/or induce insulin resistance in peripheral tissues, thus causing a rise in blood glucose levels. However, the intravenous doses used in these experimental studies were very high, ranging from 3283.2 mg/kg per day to 436363 mg/kg per day. The typical dose of oral glucosamine supplements for treatment of arthritis is about 20 mg/kg per day. Oral dosing of glucosamine at the recommended doses will not achieve the plasma levels observed in these studies. Other authors investigating the clinical use of glucosamine supplements in animals did not find any adverse effect on blood glucose. Another recent study examined the effects of oral glucosamine in rat models sensitive to sugar-induced insulin resistance and found that oral glucosamine did not induce insulin resistance.

Two studies have investigated the effects of intravenous glucosamine infusion in healthy human volunteers. Neither study showed any effect on insulin sensitivity or plasma glucose. The findings of the present study seem to parallel those of the 2 human studies in that no effect on glucose control (HbA1c levels) was observed. The present study observed patients for 90 days; if a very mild effect developed after 90 days, it would not have been detected. However, a recent long-term (3-year) clinical trial found that glucosamine supplementation actually tended to lower plasma glucose levels in patients with knee osteoarthritis.

Since patients with diabetes are at risk for toxic effects from some of the current treatments for osteoarthritis (NSAIDs in particular), glucosamine may provide a safe alternative treatment for these patients. The present study has demonstrated that oral glucosamine supplementation does not adversely affect glycemic control when administered to patients with type 2 diabetes mellitus at doses recommended by the manufacturer.

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Nutramax Laboratories Inc (Edgewood, Md) donated the Cosamin DS and placebo capsules for this study. The

### Clinical and Demographic Patient Data

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<th>Characteristic</th>
<th>Glucosamine Group (n = 22)</th>
<th>Placebo Group (n = 12)</th>
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Corresponding author and reprints: Daren A. Scroggie, MD, 759 MDOS MMIR, 2200 Bergquist Dr, Suite 1, Lackland AFB, Lackland, TX 78236 (e-mail: Daren.Scroggie@lackland.af.mil).

REFERENCES


