Oral Glucosamine in Doses Used to Treat Osteoarthritis Worsens Insulin Resistance

TAN PHAM, MD; ANNA CORNEA, MD; KENNETH E. BLICK, MD; ALICIA JENKINS, MD; R. HAL SCOFIELD, MD

*ABSTRACT: Background:*Glucosamine is used to treat osteoarthritis. In animals, the compound is known to cause insulin resistance, the underlying abnormality in type 2 diabetes mellitus. Insulin resistance in humans taking oral glucosamine in doses used for osteoarthritis has not been studied. *Methods:* Volunteer human subjects (n = 38) without known abnormality of glucose homeostasis had fasting serum glucose, insulin, and lipids determined before and after taking 1500 mg glucosamine by mouth every day for 6 weeks. Fasting insulin and glucose were used to calculate homeostasis model assessment (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI). Vascular elasticity was measured by pulse wave analysis. The paired Student's *t* test was used to compare baseline with posttreatment values. Pearson's correlation was used to determine the relation of baseline HOMA-IR with changes in other variables. *Results:* We found a rise in HOMA-IR after 6 weeks of glucosamine (2.8 versus 3.2, $P < 0.04$). The fall in HOMA-IR among the subjects was statistically related to a higher baseline HOMA-IR by Pearson's correlation ($P < 0.01$). A rise in serum triglycerides and a rise in LDL cholesterol were statistically related to baseline HOMA-IR. Small artery elasticity fell, and the decrease was higher in those with the highest baseline HOMA-IR. *Conclusions:* Notwithstanding its efficacy remaining in question, glucosamine is widely used as treatment for osteoarthritis, which is a condition associated with both obesity and type 2 diabetes mellitus. Our data indicate that persons with underlying poorer insulin sensitivity are at risk for worsening insulin resistance and vascular function with the use of glucosamine in doses used to treat osteoarthritis. **KEY INDEXING TERMS:** Glucosamine, Insulin sensitivity, Obesity, Human. **[Am J Med Sci 2007;333(6):333–339.]**

Osteoarthritis most commonly affects the hands and the large weight-bearing joints—the hips and knees.[1] The disorder is very common such that some degree of osteoarthritis is a nearly universal finding in the very old.[2] Thus, osteoarthritis of the knee and hip is a growing problem with aging of the population and causes significant morbidity that may lead to total joint replacement.[3,4] Treatment short of joint replacement is largely symptomatic and has included physical therapy and nonsteroidal anti-inflammatory drugs. Obesity[5–10] and diabetes[11] are independent risk factors for osteoarthritis.

Glucosamine is a widely available nutritional supplement that can be obtained without a prescription in the United States. This compound has been shown to be beneficial in osteoarthritis. Randomized, placebo-controlled trials demonstrate improved exercise time and decreased pain in subjects with knee osteoarthritis.[12,13] In addition, although controversy continues, there are data to suggest that radiographic progression of knee osteoarthritis is decreased after 3 years of oral glucosamine.[14,15] Meanwhile, glucosamine is also related to glucose metabolism. Animal studies demonstrate that high doses of intravenous glucosamine induce insulin resistance,[16–20] but data are limited or negative in humans.[21–24] Furthermore, glucosamine doses used for osteoarthritis have not been studied. The mechanism of this insulin resistance probably is due in part to the cell signaling roles of glucosamine and its metabolites via the hexosamine pathway.[25] Activation of this pathway leads to insulin resistance, which is induced much more strongly by glucosamine compared with glucose. Animal and in vitro studies suggest effects in the liver on glucose production and in peripheral tissues on glucose uptake as well as in the pancreatic β-cell on insulin production.

Given the known induction of insulin resistance and known bioavailability of oral glucosamine, we

From the Endocrinology (TP, AC, AJ, RHS), Metabolism, and Diabetes Division, Departments of Medicine and Pathology (KEB), University of Oklahoma Health Science Center, Oklahoma City, Oklahoma; the Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma; and Medical Service, Department of Veterans Affairs Medical Center (RHS), Oklahoma City, Oklahoma.

Submitted August 8, 2006; accepted in revised form November 30, 2006.

Correspondence: Dr Hal Scofield, 825 NE 13th Street, Oklahoma City, OK 73104 (E-mail: hal-scofield@omrf.ouhsc.edu).

undertook this study to determine whether glucosamine given orally in doses shown to be effective in osteoarthritis worsens insulin sensitivity.

Methods

Normal subjects were recruited to take part in the study, which was conducted in the University of Oklahoma Health Sciences Center General Clinical Research Center (GCRC). The study was approved by the institutional review board, and each subject underwent informed consent. Inclusion criteria included age from 18 to 80 years, no personal history of diabetes, and no personal history of polycystic ovarian disease. Exclusion criteria were myocardial infarction within the last 6 months, taking medication within the previous 6 weeks known to affect glucose metabolism, and past use of glucosamine within 1 year. The subjects underwent a complete history and physical examination and had an HgbA1c measured to eliminate persons with undiagnosed diabetes. On day 0 of the trial, fasted subjects had blood obtained for glucose, insulin, and serum lipids. On days 1 through 42, the subjects took 1500 mg glucosamine by mouth every day. At days 14 and 28, subjects returned to the GCRC for issuance of medication and pill count. On day 43, the subjects returned the GCRC for repeat studies. At the day 0 and day 43 visits, each subject had small and large artery elasticity measured by pulse wave analysis (CVProfilor, Hypertension Diagnostic, Inc, Eagan, MN), as previously reported.[26,27] Serum lipids, including the typical clinical parameters plus additional measures such as HDL and LDL triglycerides, were measured by methods previously reported.[28]

Because of the design of the study with paired results before and after the intervention, a paired Student's t test was used for statistical analysis. HOMA-IR and QUICKI were calculated as previously described.[29,30] Pearson's correlation was used to assess the relation of baseline HOMA with the change in variables, including HOMA and serum triglycerides.

Results

Demographic data are shown in Table 1. As can be seen, 7 subjects had fasting serum insulin levels above the normal range. A higher body mass index (BMI) was strongly associated with a higher HOMA, as expected (not shown). There was no change in BMI or HGBA1c during the 6 weeks of glucosamine; however, serum insulin levels rose (Figure 1). Consistent with the rise in insulin, we found that there was a statistically significant rise in HOMA after 6 weeks of glucosamine therapy, with average baseline HOMA of 2.8 and average final HOMA of 3.2 ($P = 0.04$, see Figure 1). QUICKI, a mathematical measure of insulin sensitivity that is inversely related, also showed a significant fall, consistent with worsening insulin resistance (data not shown).

Table 1. Demographics of Glucosamine Study Subjects

Age		
Average	43.9	
Range	23–67	
Sex		
Male	18	
Female	20	
BMI*	Pretrial	Posttrial
Average	29.1 ± 7.35	28.7 ± 7.03
Range	19.2–46.3	19.1–45.9
Insulin†	Pretrial	Posttrial
Average	11.7 ± 4.8	12.95 ± 5.3
Range	3.2–30.1	3.7–35.4
HGBA1c	Pretrial	Posttrial
Average	5.54 ± 0.74	5.45 ± 0.51
Range	4.50–5.30	4.30–6.80

For selected parameters, values before (pretrial) and at the end of (posttrial) 6 weeks of glucosamine are given.
**Fourteen subjects <25, 9 subjects >25 to <30, and 15 subjects >30.*
†Seven subjects had insulin above the normal range.

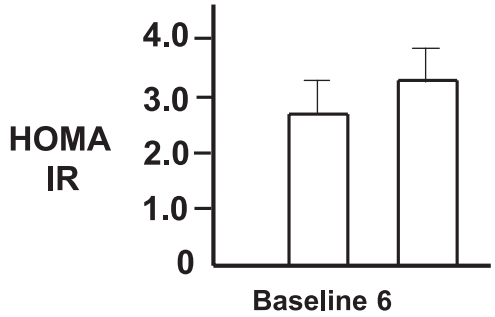

Figure 1. Baseline HOMA and HOMA after 6 weeks of 1500 mg glucosamine PO every day in the 35 subjects. The average at baseline was statistically different from that after 6 weeks of glucosamine ($P = 0.04$ by Student's t test).

We hypothesized that those with baseline insulin resistance would have the greatest effect on glucose metabolism by glucosamine. When examined individually, 25 of 35 subjects had a rise in the HOMA and a fall in QUICKI after the 6 weeks of daily glucosamine, compared with baseline values. Those patients who did not have a rise in HOMA were statistically more likely to have a lower baseline HOMA ($P = 0.01$ by Wilcoxon rank testing). Therefore, we examined the influence of baseline HOMA on the change in HOMA or QUICKI, as well as other parameters. We found that those with the highest baseline insulin resistance as measured by HOMA had the greatest change in HOMA or QUICKI, with the change in QUICKI reaching statistical significance (Figure 2).

When examining individual subjects' change in serum lipids from baseline to the end of the trial, we noted that some subjects had a marked elevation of triglyceride or LDL cholesterol. Similar to the data found for baseline HOMA and change in HOMA/QUICKI, we found that the changes in triglyceride or LDL cholesterol levels were related to baseline HOMA in that those with the highest starting HOMA values had the largest changes in serum triglyceride. Although this was true for total serum triglyceride, the data were particularly striking for LDL triglyceride and LDL cholesterol (Figure 3).

Likewise, the measurement of small artery elasticity, which is related to insulin sensitivity,[31–33] by pulse wave analysis varied with baseline HOMA. We found that in the subjects who entered the trial