Supplementation with Glucosamine Has no Adverse Effects on Glycemic Level and Insulin Resistance in Type 2 Diabetic Patients

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Abstract

Background: Use of glucosamine as an alternative treatment for osteoarthritis is becoming more frequent, including in those who have diabetes at the same time. The results from in vitro and animal studies propose that glucosamine may inversely affect glucose metabolism. However, the recommended dose of oral glucosamine in healthy people or diabetics did not have such effects consistently. The aim of the present study was to assess the effect of glucosamine on glycemic control and insulin resistance in type 2 diabetic patients.

Methods: Fifty-four patients with type 2 diabetes participated in this randomized, double-blind, placebo-controlled study. The participants were assigned to receive 1500 mg glucosamine hydrochloride or placebo for 12 weeks. After determining their baseline characteristics, body mass index and dietary intake components, fasting blood glucose and fasting insulin were measured at weeks of 0, 8, and 12. Indices of insulin function including quantitative insulin sensitivity check index (QUICKI) and homeostasis model assessment of insulin resistance (HOMA-IR) were calculated by specific formulas. Independent t-test and general linear model repeated measures were used to analyze the data.

Results: In the glucosamine group, the means of fasting blood glucose and insulin were 107.31±24.07 mg/dl and 8.75±4.37 µu/ml, respectively at baseline, which reached 112.38±31.50 and 9.10±4.17 at week 12. In the placebo group, the mean for fasting blood glucose and insulin were 103.84±24.15 and 9.79±4.02 at the beginning of the study, which reached to 111.40±26.43 and 8.58±3.68 at week 12. The results showed that there were no significant differences in fasting blood glucose, insulin, HOMA-IR and QUICKI indices at all the studied time points (weeks of 0, 8 and 12) within or between the groups.

Conclusion: Twelve weeks of a normal recommended dose of glucosamine supplements may not have adverse effects on glycemic control and insulin resistance in type 2 diabetic patients.

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Introduction

Diabetes is a metabolic disorder identified with hyperglycemia associated with disorders in insulin secretion or insulin function.[1] Type 2 diabetes, as the predominant type of the disease, is prevalent in the aged

population.[2] Osteoarthritis is also the most widespread type of arthritis, specially affecting the elderly people.[3] So this can make diabetes and osteoarthritis oftentimes overlap.[4] Moreover, genetics, obesity and sedentary lifestyles are the risk factors that make individuals more susceptible to these two diseases.[3,5]

Conventional therapies for osteoarthritis, like non-steroidal anti-inflammatory drugs (NSAIDS) have considerable adverse effects[6] such as gastrointestinal complications, and cardiovascular problems.[7] Although selective cyclooxygenase-2 inhibitors have reduced gastrointestinal adverse effects compared to non-selective NSAIDs, they may be associated with increased cardiovascular problems.[7] Inasmuch as old people with type 2 diabetes frequently have comorbidities which exacerbate the side effects of NSAIDS, many of them may try dietary supplements as alternative treatments.[4]

Glucosamine (2-amino-2-deoxy-D-glucose), an amino monosaccharide, is a normal component of glycosaminoglycans which integrate into cartilage matrix, synovial fluid, mucous secretions, connective tissue, skin, tendon and ligaments.[6,8,9] It may have different pharmacological effects on the articular cartilage and joint tissues.[8]

The theory of using glucosamine for relieving the symptoms of osteoarthritis was originated due to its high concentration in the joint tissues.[6] Many clinical trials have investigated this theory and nowadays glucosamine supplements are consumed to alleviate arthritic symptoms to a great extent.[6,10] Since osteoarthritis and diabetes are two common chronic diseases that may occur concurrently, awareness about the normal and recommended dose of glucosamine supplements on glucose control and metabolism is essential.[11]

Glucosamine may potentially alter glucose control through two suggested mechanisms.[11] The first mechanism regards glucosamine as a source of glucose as it is a metabolic product of glucose. But the conversion of glucosamine to glucose is improbable in humans since the related enzymatic pathway is irreversible.[4,11] Interference of the exogenous glucosamine with hexosamine biosynthesis pathway is the second proposed mechanism.[11] It is suggested that the pathway has a regulatory role in glucose homeostasis in humans.[12] In normal cellular states[4], when intracellular energy requirements are fulfilled, glucose metabolism switches to the hexosamine pathway.[11] Endogenous glucosamine is produced from fructose 6-phosphate and glutamine by the rate-limiting enzyme named glutamine:fructose-6-P-amidotransferase.[4,13] Based on experimental models, the shift of glucose metabolism to the hexosamine biosynthetic pathway functions as a signal, concerning the adequacy of intracellular glucose levels.[4] This results in reducing the cellular uptake of glucose[11], through down-regulating glucose transporters.[4] In this way, it is suggested that the hexosamine pathway that accounts for a small amount of glucose utilization, acts as a fuel detector for insulin sensitive cells. Thus, when the cells are filled up with substrates, insulin resistance progresses.[14] It has been proposed that elevated biosynthetic activity within the hexosamine pathway is associated with progression of insulin resistance.[15] As a matter of fact, it has been indicated that a flux of surplus substance into the hexosamine pathway by different means comprising routing of entering glucose or glucosamine via the hexosamine pathway and/or intracellular aggregation of glucosamine metabolites[12,15] stimulates defects in insulin-induced glucose uptake, glut 4 translocation[15] and activation of glycogen synthase.[12,15] However, the mechanism of impairing insulin function by glucosamine and early sequence of incidents leading to peripheral insulin resistance is still indefinite.[15]

The results obtained from in vitro and animal studies propose that glucosamine may inversely affect insulin sensitivity and metabolism of glucose.[11,16] However, in isolated and cultured cell models the investigated mean concentrations of glucosamine were 200-500 times more than serum concentrations of humans expected after usual oral doses of glucosamine (0.06 mmol/L).[6,11] Moreover, high levels of glucosamine infusion resulted in elevation of plasma glucose levels in animals.[4] However, normal, recommended dose of oral glucosamine in healthy or diabetic humans did not have such effects consistently.[11]

There are only few studies which have directly determined the effect of usual and recommended dose of glucosamine (1500 mg/day) on glucose control in diabetics.[4,17] Therefore, we conducted a placebo-controlled, double-blind clinical trial to investigate the effect of glucosamine hydrochloride on fasting blood glucose, insulin, and insulin resistance in type 2 diabetic patients.

Methods

Participants

Fifty-eight patients with type 2 diabetes aged between 40 and 79 years were recruited from Motahari and Naderkazemi medical centers in Shiraz, Iran through convenience sampling method in 2011. All participants were diagnosed with type 2 diabetes mellitus and had fasting blood glucose level of <150 mg/dl. The diagnosis criterion for having diabetes was having fasting plasma glucose ≥126 mg/dl that was confirmed on a subsequent day by repeating the test. The participants underwent treatment with a constant dose of oral hypoglycemic medications. Patients on insulin therapy and those with unstable blood glucose levels were excluded from the study. Taking any medications or supplements which interfere with

glucose metabolism (such as glucocorticoids), having shellfish allergies, having history of cardiovascular diseases, myocardial infarction and thyroid problems were other exclusion criteria of this study.

The study protocol was approved by the ethics committee of Shiraz University of Medical Sciences. Informed consent was obtained from each participant and they were provided with written and verbal explanation of the study.

Experimental Protocol

The current study was a randomized, double-blind and placebo-controlled clinical trial. The participants were assigned to the treatment and control groups. Twenty nine patients were allocated in each group. The treatment group received 1500 mg glucosamine hydrochloride (Vitamin World, U.S.A) while the other group received placebo (calcium phosphate) once a day for 12 weeks. Before the study, a 24-hour dietary recall was filled out for each patient and energy content of the diets and percentage of energy derived from macronutrients were calculated from them. Subsequently, all patients filled out a questionnaire and their weights and heights were determined. Weight was measured using an analog scale (Seca), while patients were in light clothes and had no shoes on. Height was determined using a stadiometer. Body mass index (BMI) was obtained by dividing their weight (in kilogram) by the square of the height (in meter). Baseline serum samples were drawn for analysis of fasting blood glucose and serum insulin levels after 12 hours of fasting.

Patients were visited fortnightly at medical centers and received glucosamine supplements or placebo for the following 2 weeks. Moreover, they were asked to continue their baseline diabetic medications and report any changes to the researcher.

After baseline measurements, fasting blood glucose and serum insulin levels were measured at weeks of 8 and 12. Blood glucose analysis was performed by the enzymatic colorimetric method on autoanalyzer. Insulin analysis was done using DRG insulin ELISA kit (EIA 2935, DRG Instruments GmbH, Germany). The Kit is a solid phase enzyme-linked immunosorbent assay (ELISA) according to sandwich method. Indices of insulin function including HOMA-IR and QUICKI were determined at all the time points. HOMA-IR was calculated according to the formula: fasting insulin (μu/mL) x fasting glucose (mmol/L)/22.5 and QUICKI index was determined using the formula: 1/ [log (glucose mg/dl)+log (insulin μu/ml)].[18] The flow chart of the study is illustrated in Figure 1.

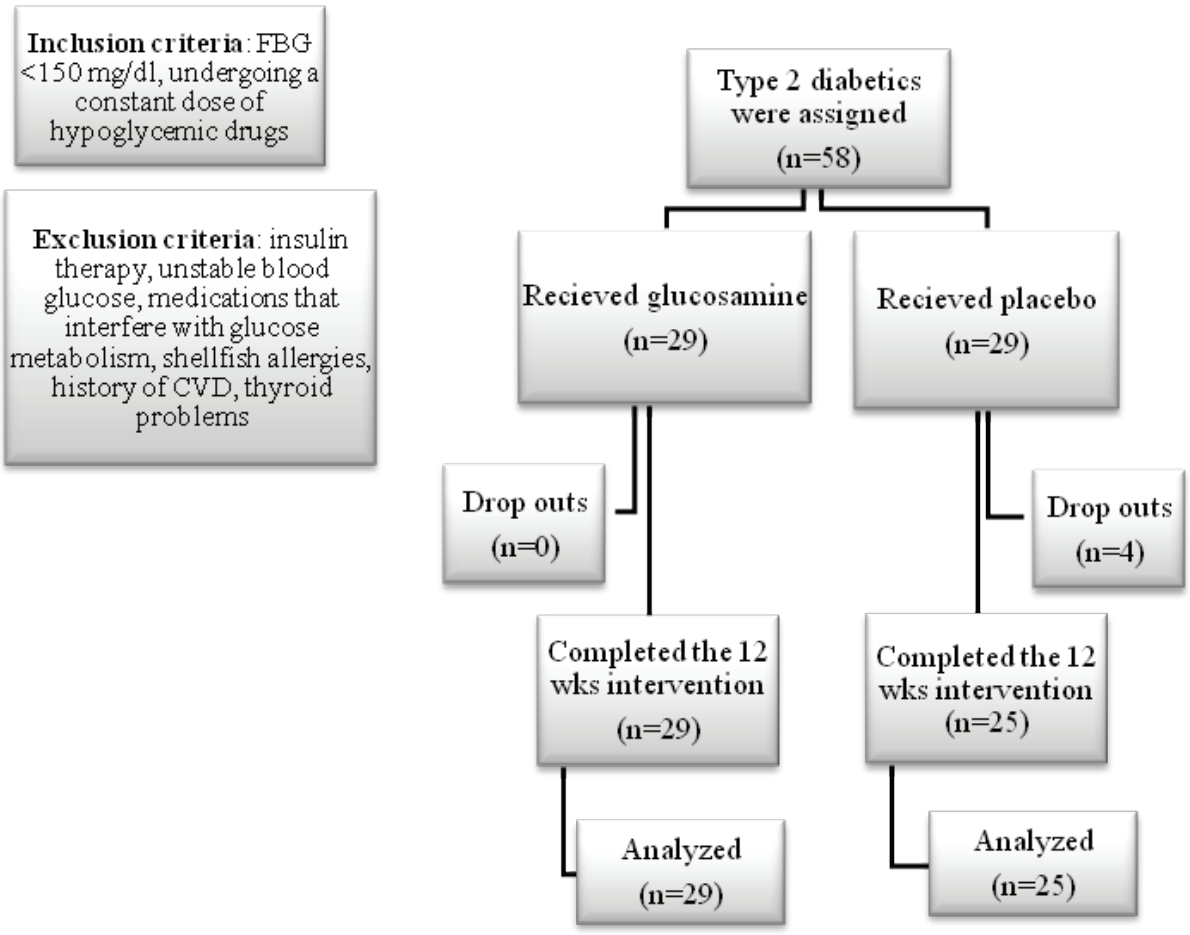

Figure 1: Flowchart of diabetic patients receiving glucosamine or placebo for 12 weeks.

Statistical Analysis

Statistical analysis was performed using SPSS software (ver. 16). Independent t-test was used to compare the means of baseline characteristics and dietary components between the groups. General linear model repeated measures and t-test were applied to compare biochemical variables in the groups. Chi-square test was also used to compare the genders between the groups. A P value<0.05 was considered statistically significant.

Results

Baseline Characteristics

Fifty-four participants (29 patients in the glucosamine group and 25 patients in the placebo group) completed the study and four of them (in the control group) withdrew from the trial, since they were not willing to continue their participation in the intervention. The mean age of the participants was 54.90±9.62 (range 40-79) and the mean BMI was 28.87±4.10 (range 21.56-39.26). See Table 1 for subject characteristics.

The mean values for sex, age, duration of the disease, education, BMI, and number of daily used glibenclamide tablets at baseline were not significantly different between the groups. However, the mean number of metformin tablets taken in the glucosamine group was significantly higher than the placebo group (P=0.027) (Table 1).

Comparing the dietary intake of the participants showed that there were no significant differences regarding energy and protein intakes between the groups. However, energy intake derived from carbohydrate was significantly higher in the placebo group (P=0.033) and energy intake derived from fat was significantly lower in the placebo group (P=0.039). But it should be considered that all the energy percentages derived from these macronutrients were within the recommendations (Table 2).

Biochemical Parameters

In the glucosamine group, the means for fasting blood glucose and insulin levels were 107.31±24.07 mg/dl and 8.75±4.37 µu/ml respectively at baseline, which reached 112.38±31.50 and 9.10±4.17 at week 12. In the placebo group, the means for fasting blood glucose and insulin were 103.84±24.15 and 9.79±4.02 at the beginning of the study, which reached 111.40±26.43 and 8.58±3.68 at week 12.

No significant differences were observed in the mean values of fasting blood glucose, fasting serum insulin, HOMA-IR and QUICKI indices at weeks of 0, 8 and 12 between the groups. Furthermore, there were no significant differences in the mean of these biochemical variables within the three time points of each group (Table 3). The mean values of

Table 1: Baseline characteristics of the participants in the glucosamine and placebo groups

Characteristic		Glucosamine (n=29)	Placebo (n=25)	P value
Sex (F/M)		20/9	21/4	0.198
Age (year)		55.89±8.57	53.80±10.74	0.435
Duration of type 2 diabetes (year)		5.00±3.54	4.31±4.19	0.521
Education (year)		7.25±5.71	5.37±4.98	0.217
BMI (kg/m^2)		28.76±3.59	29.00±4.69	0.830
Number of oral hypoglycemic medications	Glibenclamide	1.78±1.56	1.31±1.37	0.259
	Metformin	2.21±1.40	1.36±1.33	0.027†
	Glucobay	0.22±0.70	0	-----

Data are reported as mean±SD, when appropriate. Chi square test for comparison of genders and independent sample t-test for comparison of other variables between the groups. †Significant (P<0.05)

Table 2: Comparison of dietary intakes of the participants between glucosamine and placebo groups

Variable	Glucosamine	Placebo	P value*
Energy (Kcal)	1783.37±217.24	1770.09±284.62	0.854
Carbohydrate (%)	55.11±3.70	57.36±3.37	0.033†
Protein (%)	18.00±1.66	17.59±1.14	0.332
Fat (%)	26.93±3.27	25.09±2.65	0.039†

Values are reported as mean±SD. *Independent sample t-test; †Significant (P<0.05)

Table 3: Comparison of the biochemical variables in the glucosamine and placebo groups at the three time points

Variable	Glucosamine (n=29)				Placebo (n=25)			
	Baseline	Week 8	Week 12	P value*	Baseline	Week 8	Week 12	P value
Fasting glucose (mg/dl)	107.31±24.07	103.31±25.21	112.38±31.50	0.20	103.84±24.15	114.64±30.30	111.40±26.43	0.06
Fasting insulin (µu/ml)	8.75±4.37	8.78±3.72	9.10±4.17	0.72	9.79±4.02	9.37±4.40	8.58±3.68	0.25
HOMA-IR	2.25±1.04	2.10±0.73	2.46±1.20	0.36	2.53±1.23	2.74±2.14	2.33±1.24	0.52
QUICKI Index	0.35±0.04	0.35±0.02	0.34±0.03	0.95	0.34±0.04	0.34±0.02	0.34±0.03	0.70

*General linear model repeated measures

HOMA-IR, QUICKI and fasting serum insulin at 3 time points of both groups were <2.6, >0.33 and <12 µu/dl except for HOMA-IR at week 8 of the placebo group. Patients were considered as insulin resistant when HOMA-IR ≥2.6, QUICKI ≤0.33 and fasting serum insulin ≥12 µu/dl.

Discussion

The present study determined the effect of a normal dose of oral glucosamine on glycemic control and insulin resistance in type 2 diabetic patients. Findings of this study showed that there were no significant differences between or within groups in terms of fasting blood glucose, fasting serum insulin, HOMA-IR and QUICKI indices.

The results of the present study suggest that consumption of recommended dose of glucosamine has no adverse effects on glucose control or insulin function in type 2 diabetic patients. So the intervention might not provide adequate glucosamine to raise the flux through the hexosamine pathway and overload the system.

Many experimental studies have been done to assess the effect of exogenous glucosamine on glycemic control.[4] However, comparing the results of these studies with the current study is difficult, since in most of the previous studies high levels of glucosamine have been infused into cultured cells or have been injected intravenously into rodents for a short duration.[12] Findings of those of in vitro and animal studies reveal that glucosamine may negatively affect insulin sensitivity or glucose metabolism.[11]

Based on in vitro studies, elevation of glucosamine concentrations has resulted in some changes including glucose transport, glycogen synthesis and insulin secretion response to high glucose levels.[11] In such studies, the applied concentrations of glucosamine were 200 to 500 folds more than the serum levels obtained subsequent to oral normal doses of glucosamine in humans (0.06 mmol/l).[6,11] Furthermore, the mean of effective dose for a 50% change (ED_{50}) was >100 times more than the anticipated serum concentration following oral glucosamine administration in humans.[6] Therefore, interpreting the clinical connection of these results to the therapeutic supplementation of glucosamine in humans is hard.

Intravenous administration of glucosamine in animals has reduced insulin secretion and resulted in insulin resistance.[11] But it should be noted that oral glucosamine's bioavailability is just 26% of intravenously administered glucosamine,[6] and its serum level after consuming the oral doses is merely 20% of the level following intravenous injection. Besides, the normal dose of oral glucosamine administered for curing osteoarthritis is 23 mg/kg/day.[6,11] It is just 0.25% of the doses used to stimulate changes in glucose metabolism.[6] Thus it is difficult to attribute these data to humans regarding the effect of normal and recommended dose of glucosamine.

Glucosamine consumption is widely frequent[11] and some studies have directly assessed the effects on glucose regulations in humans. In two studies on healthy participants, glucosamine infusion was applied to speed up hexosamine pathway and the changes in glucose metabolism were evaluated.[19,20] In the first study, Pouwels and colleagues showed that glucosamine infusion up to 5 hours could not alter insulin-induced glucose uptake.[19] However, in the second study, acute glucosamine infusion repeated some metabolic characteristics of diabetes in humans, including elevation of plasma fasting glucose concentration.[20] It is not possible to interpret the findings of these studies, due to the small number of participants, as well as injection of glucosamine which leads to quick entrance into blood flow.[12]

Among those studies that assessed orally administered glucosamine, Reginster and colleagues conducted a 3 year trial, in which osteoarthritic patients ingested 1500 mg glucosamine sulfate once a day to assess the progression of joint structural changes. They observed that in patients receiving glucosamine, fasting plasma glucose slightly reduced.[8] Ingestion of 1500 mg/day glucosamine sulfate for 12 weeks in healthy participants did not change insulin and plasma glucose levels during oral glucose tolerance tests, as well hemoglobin A_{1c} (HbA_{1c}) levels.[12] Besides, findings from an uncontrolled study on obese and lean subjects indicated that administrating 1500 mg/day oral glucosamine sulfate for 4 weeks had no effects on fasting plasma glucose, insulin levels, and glucose tolerance as well as insulin sensitivity.[10] Obviously, in these three studies no deterioration in markers of glycemic control were observed following glucosamine supplementation, which is similar to the findings of the present study. However, in a study on patients with osteoarthritis, 1500 mg glucosamine sulfate supplementation during a 3-hour oral glucose tolerance test resulted in a significant rise in glucose levels of three participants with abnormal glucose tolerance. In addition, a non-significant elevation in the mean of glucose levels was observed in the other patients. However, the intervention did not alter insulin levels.[21]

Except to the current study, only two studies were found that assessed glucosamine effects on diabetic patients. One of the studies was a double-blind, placebo-controlled and randomized trial conducted by Scroggie and colleagues that has evaluated the effects of glucosamine-chondroitin supplement for 90 days in type 2 diabetics. They observed no alteration in HbA_{1c}

mean values at the end of intervention.[4] In addition, in a double-blind, placebo-controlled, and cross-over study on type 1 and type 2 diabetics with low HDL-C levels, supplementing of 1500 mg glucosamine for two weeks did not change fasting plasma glucose and fructosamine levels.[17] Observing no adverse effects in our study is in agreement with these two trials. In addition, the present study considered insulin levels and parameters of insulin resistance that were not assessed in these studies; these are the strong points of this work.

Besides, a previous systematic review conducted in 2011 analyzed glucosamine effects on metabolism of glucose in humans. The data were obtained from eleven studies. In four of them, reduced insulin sensitivity or elevated fasting glucose was found. They reported that studies with participants who were insulin resistant or who had baseline impaired glucose tolerance had a higher possibility for these negative effects. The review recommended carrying out more studies for a deterministic conclusion.[16]

The present study had some limitations. Short duration of the intervention was one of the limitations. Future studies are required to evaluate the effects of glucosamine supplementation for longer periods of time, because many elderly osteoarthritic diabetic subjects are prolonged users of glucosamine. Moreover, participants of this study had well-controlled diabetes. So it doesn't provide definitive conclusions for glucosamine effects in more severe diabetes which necessitates conducting studies in these patients. Furthermore, fasting insulin, HOMA-IR and QUICKI indices are surrogate methods for determining insulin resistance. Hence, if applicable, using hyperinsulinemic euglycemic glucose clamp as the gold standard method[22] may be suggested. Measuring plasma glucosamine levels or metabolites of hexosamine biosynthesis are other recommendations for future works which were other limitations for this work.

Conclusion

In conclusion glucosamine supplementation with a normal recommended dose for twelve weeks may not have adverse effects on glucose metabolism and insulin resistance in type 2 diabetic patients.

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Conflict of Interest: None declared.

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