Nutrition 31 (2015) 119–126

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Effect of glutamine supplementation on cardiovascular risk factors in patients with type 2 diabetes

Asieh Mansour M.Sc. [a,b], Mohammad Reza Mohajeri- Tehrani M.D. [b], Mostafa Qorbani Ph.D. [c,d], Ramin Heshmat M.D., Ph.D. [e], Bagher Larijani M.D. [b,f], Saeed Hosseini M.D., Ph.D. [b,*]

[a] School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
[b] Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran
[c] Department of Public Health, Alborz University of Medical Sciences, Karaj, Iran
[d] Non-Communicable Diseases Research Center, Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran
[e] Chronic Diseases Research Center, Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran
[f] Diabetes Research Center, Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article history:
Received 13 January 2014
Accepted 24 May 2014

Keywords:
Glutamine supplementation
Type 2 diabetes
Body composition
Insulin
GLP-1

ABSTRACT

Objective: The aim of this study was to assess clinical relevance of long-term oral glutamine supplementation on lipid profile and inflammatory and metabolic factors in patients with diabetes.
Method: Sixty-six patients with type 2 diabetes between the ages of 18 and 65 y were randomized to receive glutamine 30 g/d (10 g powder, three times a day) or placebo, in a double-blind, placebo-controlled trial during a 6-wk treatment period. Fifty-three patients completed the trial. Independent samples *t* test and analysis of covariance were used.
Results: After a 6-wk treatment period, a significant difference was observed between the two groups in body fat mass ($P = 0.01$) and percentage of body fat ($P = 0.008$). Moreover, a significant reduction in waist circumference ($P < 0.001$) and a tendency for an increase in fat-free mass ($P = 0.03$), with no change in body weight and body mass index (BMI) was found. Enhancement in body fat-free mass was mainly attributed to trunk ($P = 0.03$). There was a downward trend in systolic blood pressure ($P = 0.005$) but not diastolic. Fasting blood glucose (mmol/L) concentration significantly decreased after the 6-wk intervention ($P = 0.04$). Mean hemoglobin A_{1c} was significantly different between the groups at week 6 ($P = 0.04$). No significant difference was detected for fasting insulin, homeostasis model assessment for insulin resistance and quantitative insulin sensitivity index between groups ($P > 0.05$). No significant difference was observed between groups in total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglyceride. No treatment effect on C-reactive protein was found ($P = 0.44$).
Conclusion: We demonstrated that the 6-wk supplementation with 30 g/d glutamine markedly improved some cardiovascular risk factors, as well as body composition, in patients with type 2 diabetes. Future glutamine dose–response studies are warranted in these areas.

Introduction

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia resulting from defects in insulin secretion or action [1] and corresponds to 1.7% of total world mortality [2]. Type 2 diabetes is a major risk factor for cardiovascular disease (CVD) development [3]. On the other hand, CVD is a major cause of morbidity in individuals with diabetes [4] and more than 75% of the type 2 diabetes population

AM was responsible for the conception and design of the study; generation, collection, assembly, analysis, and interpretation of data; drafting and revision of the manuscript; and approval of the final version of the manuscript. MRM-T and SH participated in the design of the study; revision of the manuscript; and approval of the final version of the manuscript. MO was involved in the analysis and interpretation of data and approval of the final version of the manuscript. RH was involved in the design of the study. BL participated in the revision of the manuscript.

* Corresponding author. Tel.: +98 21 882 20038; fax: +98 21 882 20052.
E-mail address: saeedhmdphd@hotmail.com (S. Hosseini).

0899-9007/$ - see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nut.2014.05.014

has metabolic syndrome [5]. The rate of diabetes has risen in parallel with the increased prevalence of obesity [6]. One study [7] concluded that modest weight losses of 5% to 10% are associated with significant improvements in CVD risk factors in overweight and obese individuals with type 2 diabetes. Type 2 diabetes is associated with decreased lean body mass and increased body fat mass compared with nondiabetics with similar body mass index (BMI) values [8]. Insulin resistance may accelerate development of sarcopenia [9] and type 2 diabetes is an important predictor of this condition [8]. Excessive loss of muscle mass in type 2 diabetes may result in lower skeletal function, strength, and quality [10].

Glutamine, a nonessential amino acid is the most abundant free amino acid in circulation [11] and pool in skeletal muscle [12]. Interestingly, the circulating glutamine concentration is reduced significantly in patients with type 2 diabetes compared with healthy individuals [13]. Glutamine supplementation increases protein synthesis in catabolic stress situations [14] and decreases proteolysis in rats [15]. Studies support the hypothesis that administration of additional glutamine represents an effective dietary strategy to improve glycemic control in patients with type 2 diabetes and may be useful as an antiobesity and antidiabetic agent [16,17]. However, these hypotheses are based on small trials with single doses, some with very short study durations, or in animal models. These drawbacks mean that well-conducted randomized controlled trials are warranted for definite results. Therefore, the aim of present study was to investigate whether 6 wk of oral glutamine supplementation with each main meal (30 g/d) would induce and sustain improvement of CVD risk factors, such as hyperlipidemia, hyperglycemia, high blood pressure (BP), insulin sensitivity, waist circumference (WC), body weight, and body composition in individuals with type 2 diabetes. To the best of our knowledge, this is the first placebo-controlled trial to assess clinical effects of such long-term glutamine supplementation in patients with diabetes.

Methods

Study population

Individuals with type 2 diabetes were recruited from the diabetes clinic of Shariati Hospital, Tehran. Exclusion criteria were history of drug abuse; BMI $\geq$35 kg/m^2; current insulin therapy; history of cancer; treatment with anti-inflammatory drugs, corticosteroids, hormones, or antibiotic agents; a restrictive diet or weight change $\geq$5 kg during the 3 mo before study; systolic blood pressure (SBP) $>$ 160 mm Hg and/or diastolic blood pressure (DBP) $>$ 90 mm Hg; fatty liver disease; liver or kidney diseases; autoimmune diseases; pregnancy and lactation; any changes in treatment with oral hypoglycemic, antihypertensive, and antihyperlipidemic agents during the study; and use of weight loss medications.

The present study was approved by the medical ethics committee of Tehran University of Medical Sciences and participants signed an informed consent.

Materials and methods

Study design

Participants between the ages of 18 to 65 y who attended Shariati Hospital were randomly assigned to two groups that received either glutamine or placebo for 6 wk. The patients in each group took glutamine in free form (99.99% pure) 30 g/d (10 g powder, three times a day) or resistant starch powder from corn as placebo 3 g/d (1 g powder, three times a day), 5 to 10 min before each main meal (breakfast, lunch, and dinner) in half glass of ice-cold water [18] for 6 wk.

Diet and physical activity

To assess potential changes in daily food consumption and physical activity during the 6-wk intervention, participants kept a 3-d food record and a record of their physical activity at baseline and at week 6 of the intervention. All participants were asked to maintain their usual dietary intake and habitual physical activity for the duration of trial.

Assessments

Anthropometric measurements, body composition, and blood pressure

Patients height was measured to the nearest 0.5 cm using a wall-mounted stadiometer. Weight and body composition were measured using Tanita BC 418 MA Segmental Body Composition Analyzer (Tanita, Japan) in light clothes and not wearing shoes [19]. BMI was calculated as body weight (kg) divided by the square of height (m^2). Waist circumference was measured to the nearest 0.1 cm, midway between the lateral lower rib and the iliac crest with the patient standing upright. SBP and DBP were measured using a standard calibrated mercury sphygmomanometer on the right arm of the subjects after 5 min of rest.

Diet and physical activity measurements

Total energy and macronutrient content were calculated using Nutritionist IV software (First Data Bank, The Hearst Corporation, San Bruno, CA). Physical activity was calculated by multiplying metabolic equivalent of task and duration (h) per day using the international physical activity questionnaire [20].

Blood sampling

After a 10- to 12-h fast, blood samples were taken at baseline and at week 6 of the intervention. Serum and EDTA tubes were centrifuged at 2500*g* for 15 min. Serum and plasma were immediately frozen and stored at –80°C until further analysis. Serum concentrations of glucose, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine, and highly sensitive C-reactive protein (CRP) were measured by a colorimetric method using Pars Azmoon kits (Pars azmoon.co, Tehran, Iran) with an auto-analyzer (Autoanalyzer Hitachi 902, Roche Diagnostics, Holliston, MA, USA). Serum insulin concentration was measured by an enzyme-linked immunosorbent assay kit (Monobind kit, Monobind Inc., Lake Forest, CA, USA). Plasma concentration of hemoglobin HbA_{1c} was measured using automatic analyzer DS5 and DS5 Pink Reagent kits. The plasma concentration of glutamine was determined by high-performance liquid chromatography.

Insulin resistance was calculated by using the homeostasis model assessment (HOMA-IR) method [21]: fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5. Insulin sensitivity was calculated by using the quantitative insulin sensitivity check index (QUICKI) method [22]: 1/[log insulin (μU/mL) + log glycemia (mg/dL)].

Statistical analysis

Statistical analyses were performed by SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Independent samples *t* test was used to compare any differences between the two groups at the baseline. Within-group comparisons were analyzed by the paired *t* test. Analysis of covariance utilizing a general linear model, was used to test the difference between study groups at the end of study. $P < 0.05$ was considered statistically significant.

Results

Sixty-six individuals with type 2 diabetes were randomly assigned to either a glutamine or a placebo group for 6 wk. Fifty-three individuals completed the trial and were included in the statistical analyses, 27 in the glutamine group and 26 in the placebo group (Fig. 1). Baseline characteristics for glutamine and placebo groups are shown in Table 1. With the exception of DBP, which was lower in the glutamine group ($P = 0.03$), no significant differences were observed between the groups at baseline (fig. 4B).

When the 3-d food records and physical activity questionnaires were analyzed, the glutamine and placebo groups were similar in intakes of macronutrients, energy (Table 3), and