Effects of L-Carnitine on Glycemic Control and C-Peptide Levels in Patients with Type 2 Diabetes Mellitus

Tip 2 Diyabetik Hastalarda L-Karnitinin Glisemik Kontrol ve C-Peptid Üzerine Olan Etkileri

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Abstract

Objective: This study investigates the effects of L-carnitine on glycemic control in non–insulin-dependent patients with diabetes mellitus.

Materials and Methods: The effects of L-carnitine on levels of blood glucose and C-peptides were studied in 25 women and 35 men with type 2 diabetes mellitus, with an average age of 53.3 years. Patients were randomized to either the L-carnitine or the placebo group. During a 3-month period, 1 g oral L-carnitine or placebo was administrated 3 times a day (3 g/day).

Results: A significant reduction was observed in the fasting blood glucose level in the L-carnitine group at Week 12 (end of study) compared with the level at baseline: 143.93 ± 34.74 mg/dL and 129.43 ± 32.16 mg/dL, respectively ($p < 0.05$). No significant changes were observed in either group for concentrations of 2-hour postprandial blood glucose, hemoglobin A1C, or C-peptides.

Conclusions: L-carnitine significantly reduced the fasting blood glucose level at Week 12 but had no effect on 2-hour postprandial blood glucose levels, hemoglobin A1C concentrations, or C-peptide levels in patients with non–insulin-dependent diabetes mellitus. *Turk Jem 2008; 12: 1-3*

Key words: L-carnitine, type 2 diabetes mellitus, C-peptide levels, hemoglobin A1C concentration, pyruvate dehydrogenase

Özet

Amaç: Bu çalışma, İnsüline bağımlı olmayan diabetik hastalarda, L- kartinin'in glisemik kontrol üzerine etkilerini araştırmak üzere gerçekleşmiştir.

Gereç ve Yöntem: Yaş ortalaması 53.3 olan tip 2 diyabetik 35 erkek ve 25 kadında L-karnitinin kan şekeri ve C-peptid düzeyleri üzerine etkileri araştırıldı. Hastalar rastgele olarak L-karnitin ve plasebo olmak üzere 2 gruba ayrıldı. Her iki gruba ağızdan günde 3kez 1 gram 3 ay süreyle uygulandı.

Bulgular: L-karnitin grubunda açlık kan şekeri 3 ay içinde anlamlı düşme (143.93±34.74mg/dl'den 129.43±32.16mg/dl'ye) gösterdi. Her iki grupta 2. saat postprandial kan şekeri değeri, hemoglobin A1c ve C-peptid değeri bakımından anlamlı değişiklik gözlenmedi.

Sonuç: L-karnitin 3 ay içinde açlık kan şekeri değerlerini düşürmekle birlikte 2. saat postprandial, hemoglobin A1c ve C-peptid değerleri üzerine etkili değildir. *Turk Jem 2008; 12: 1-3*

Anahtar kelimeler: L- kartinin, tip 2 diyabet, c-peptid

Introduction

L-carnitine, L-beta-hydroxy-gamma-N-trimethylaminobutyric acid, is synthesized primarily in the liver and kidneys from the amino acids lysine and methionine. L-carnitine mediates the transport of long-chain acyl groups into the mitochondria for oxidation and transports intermediate toxic compounds from the mitochondria into the cytoplasm. Acetyl-CoA is trapped by L-carnitine by lowering the intramitochondrial acetyl-CoA/CoASH ratio, thus increasing the activity of the pyruvate dehydrogenase enzyme and stimulating glucose catabolism (1-4).

Although few human studies have been conduction on the administration of supplemental L-carnitine and its effects on glycemic control in patients with diabetes, animal studies have shown that the activity of the pyruvate dehydrogenase enzyme and glucose metabolism are decreased in diabetes (4-8). De Gaetano et al. showed that L-carnitine stimulated glucose disposal and oxidation in healthy volunteers (1). Low levels of L-carnitine have been reported in patients with type 2 diabetes (9), and researchers have shown that L-carnitine increases the activity of the pyruvate dehydrogenase complex, which increases

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glucose catabolism (9,10). Tamamoğullari et al. concluded that L-carnitine may play an important role in patients with complications of diabetes mellitus (9). Tamamoğullari and coauthors found low levels of L-carnitine in three groups of patients with long-term disease who had complications associated with type 2 diabetes compared with L-carnitine levels in one group of patients without complications. After using the euglycemic hyperinsulinemic clamp test with a simultaneous constant infusion of L-carnitine, Mingrone et al. reported that acute hypercarnitinemia stimulates nonoxidative glucose disposal in both healthy volunteers and patients with type 2 diabetes (10). Capaldo et al. also studied intravenous infusion of L-carnitine and observed improved insulin sensitivity and significantly decreased serum lactate levels in patients with type 2 diabetes (11). Only one previously reported study produced opposite results, which was carried out by Derosa et al. in a group of patients with newly diagnosed type 2 diabetes mellitus whose disease was managed through dietary restrictions only (12).
Ours is the first study to examine the effects of high-dose oral L-carnitine on glycemic control and C-peptide levels in patients who have had type 2 diabetes mellitis for a long period of time.

Materials Methods

In this double-blinded study, 60 patients with type 2 diabetes mellitus were selected from patients at the Endocrine Clinic of Hamedan University of Medical Science in Hamedan, Iran. The average age of these patients was 53.3 years, and they had diabetes for an average of 11.2±3.1 years. All study patients, 25 women and 35 men, were diagnosed according to criteria from the American Diabetes Association (ADA). Eligibility requirements included a fasting blood glucose level of less than 200 mg/dL, hemoglobin A1C concentration of less than 10%, creatinine level of less than 1.5 mg/dL, and body mass index of less than 30 kg/m^2. Patients also must have been using inhaled glibenclamide plus oral metformin as treatment for diabetes. Only nonsmoking patients without thyroid or liver disease were eligible.
The procedures of the study, their importance, and how they relate to a proper diet and physical activity were explained to all participants. All participants were provided with and signed a written informed consent form.
Patients were divided into two groups, 25 patients in the L-carnitine group and 35 patients in the placebo group, and were matched for age, sex, body mass index, and hemoglobin A1C concentration. No significant differences were observed between the two groups. "Shahr-daro" L-carnitine, 1 g 3 times a day (3 g/d), was administrated to patients in the L-carnitine group for 12 weeks. Patients in the placebo group received the same dosage of a placebo. The placebo and the L-carnitine were obtained from the same manufacturing plant.
After a 12-hour fast, a 5-mL blood sample was taken from all patients. Another 5-mL blood sample was taken from all patients at 2 hours after breakfast. Height and weight of all patients were measured using the CECA digital scale (United Kingdom), with 100-g accuracy. The Sinnowa B300 Fully Automatic Biochemistry Analyzer (Sinnowa Medical Science & Technology Co. Ltd, Italy). was used to measure both fasting and 2-hour postprandial blood glucose levels. An enzymatic method using the DRG kit was used to measure hemoglobin A1C concentrations. The Immunoturbidimetric Method RT1000 Auto Analyzer and Germany Diagnostic factory kits were used to analyze C-peptide levels. Measurements of blood glucose, hemoglobin A1C, C-peptides, and body mass index were repeated at Week 6 and Week 12 (end of study).
Specific instructions about physical activity, and especially about diet, were provided to all study participants before the first dose of study drug was administered. During the study, a telephone call was placed every 2 weeks to all participants to evaluate whether they were complying with the administration of L-carnitine or placebo and whether they were following the instructions they were provided concerning diet and physical activity. All particpants were required to return the empty drug and placebo containers.
Patients who had a weight loss of more than 2 kg in 2 weeks or who used L-carnitine or placebo improperly were not permitted to continue in the study.

Statistical Analysis

Data were analyzed using SPSS version 10, analysis of variance (ANOVA) with multiple measurements, Ben Ferny correction for comparing changes through time for variants with normal distribution, and Freidman for variants with abnormal distribution. To compare statistical changes, the t-test was used for variants with normal distribution and the Mann-Whitney U test for variants with abnormal distribution. Analysis of covariance (ANCOVA) was used to compare data at Week 6 and Week 12.
The procedures followed in this study were in accordinace with the ethical standards of the responsible committee on human experimentation.

Results

Two groups of patients, all of whom were nonsmokers, were matched for age, sex, body mass index, diet, and daily physical activity. At Week 12 of study drug administration, fasting blood glucose levels decreased signficantly ($p < 0.05$) in patients in the L-carnitine group, whereas no meaningful change occurred in the placebo group (Table 1). At Week 6, no significant differences in fasting blood glucose levels were observed between the L-carnitine and placebo groups. In addition, at Week 6 and Week 12, no significant reductions were seen in either group in 2-hour postprandial blood glucose levels, hemoglobin A1C concentrations, or C-peptide levels. No clinically relevant adverse effects were observed.

Discussion

The effects of oral L-carnitine supplements in patients with diabetes were tested, and we observed that this therapy did not influence 2-hour postprandial blood glucose levels, hemoglobin A1C concentrations, or C-peptide levels but did significantly decrease fasting blood glucose levels by 9% at Week 12. There are two main differences between our study and the study by Derosa (12). In our study, the L-carnitine dosage was 3 g/day and the patient population had a history of diabetes for at least 8 years. In the Derosa study, the L-carnitine dosage was 2 g/day and the patient population had newly diagnosed diabetes.
No significant changes were observed in the 2-hour postprandial blood glucose level after administration of L-carnitine at the beginning of our study compared with the level at the end of our study. No similar studies are available for comparison.
No signficiant changes were observed between the L-carnitine and placebo groups in our study, which is consistent with the findings by Derosa (12). At the end of our study, in the L-carnitine group, fasting blood glucose levels were significantly decreased but 2-hour postprandial blood glucose levels were not. These results could be attrib-

Table 1. Means and Standard Deviation of Concentration of FBS- 2hppBS – Hb A1C & C-peptide in Diabetic patients of L-Carnitine and placebo groups.

Parameter		Number of patients	Start	Week 6	Week 12
FBG (mg/dL)	L-carnitine	25	143.93±34.74	139.66±34.38	129.43±32.16*
	Placebo	35	149.41±32.14	152.70±45.90	159.92±74.05
2hpp BG (mg/dL)	L-carnitine	25	185.22±35.73	179.42±33.38	180.59±33.17
	Placebo	35	180.11±34.16	182.21±38.40	178.93±36.22
HbA1C (%)	L-carnitine	25	6.92±1.65	7.29±1.42	7.01±2.010
	Placebo	35	6.87±2.16	7.65±1.41	7.03±2.11
C-peptides (mg/dL)	L-carnitine	25	2.7±2.22	2.29±1.84	2.04±1.28
	Placebo	35	2.21±2.35	2.21±0.81	2.18±0.92

*Significant difference ($p < 0.05$) compared with baseline.

uted to the short timeframe of our study (12 weeks), which also could explain the lack of reduction in hemoglobin A1C concentrations.
Finally, C-peptide levels did not change signficiantly in our study. This result corresponds with the results of some studies (1,12,17) but not others (10,11). Capaldo et al. and Mingrone et al. found that the effect of L-carnitine on blood glucose is the indirect result of L-carnitine on insulin receptors and the increasing susceptibility of these receptors to insulin (10,11). De Gaetano et al. found that this reduction is the result of a post-insulin receptor defect (1). However, none of these researchers (1,10,11) found that the increase in insulin level is the result of insulin and C-peptide secretion simultaneously. Therefore, it is likely that the reduction in blood glucose levels is a direct effect of L-carnitine causing an increase in the activity of the pyruvate dehydrogenase enzyme and an indirect effect on receptors and postreceptor agents.
One weakness of our study is that blood levels of L-carnitine before and after its administration were not measured. Instead, we attempted to study the use of L-carnitine in patients with several methods that are highly accurate.
Additional studies are needed to determine the effects of L-carnitine on blood glucose levels and, simultaneously, the effects of lipids with higher doses of L-carnitine, longer courses of treatment, and a larger number of patients.

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