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ORIGINAL COMMUNICATION

Effect of L-carnitine on plasma glycemic and lipidemic profile in patients with type II diabetes mellitus

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Objective: We designed this study to investigate the effects of oral L-carnitine administration on fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c) and lipid parameters in patients with diabetes mellitus type II.
Patients and methods: The effect of L-carnitine on FPG and lipid parameters was investigated in 22 male and 13 female type II diabetic patients; the mean age $\pm$ s.d. was 51.3 ± 3.7 y. The patients were randomly allocated to two groups (L-carnitine and placebo group) and 1 g of L-carnitine or of placebo was given orally three times a day for a period of 12 weeks.
Results: FPG in the L-carnitine group decreased significantly from 143 ± 35 to 130 ± 33 mg/dl ($P = 0.03$), and we observed a significant increase of triglycerides (TG) from 196 ± 61 to 233 ± 12 mg/dl ($P = 0.05$), of Apo A1 from 94 ± 20 to 103 ± 23 mg/dl ($P = 0.02$), and of Apo B100 from 98 ± 18 to 108 ± 22 mg/dl ($P = 0.02$) after 12 weeks of treatment. There was no significant change in LDL-C, HDL-C, HbA1C, LP(a) or total cholesterol.
Conclusion: L-Carnitine significantly lowers FPG but increases fasting triglyceride in type II diabetic patients.
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Introduction

Carnitine (3-hydroxy-4-N-trimethylammonio-butanoate) is a well-established acyl group carrier into mitochondria, and in some studies it has been found to modify the lipid profile of hypertriglyceridemic and hypercholesterolemic men and animals (Fritz & Marquis, 1965; Maebashi *et al*, 1978; Vacha *et al*, 1983; Maccari *et al*, 1985; Reymond *et al*, 1987; Secombe *et al*, 1987; Rodrigues *et al*, 1988). Moreover, carnitine acts as a carrier of acetate from mitochondria to the cytoplasm, it thus reduces the acetyl CoA/CoA ratio in mitochondria, and therefore increases the activity of pyruvate dehydrogenase and consequently of glucose catabolism (Uziel *et al*, 1988; Broderick *et al*, 1992; Di Donto *et al*, 1992). However, data on the effect of oral L-carnitine on human glucose homeostasis are scarce (Yeh *et al*, 2003).

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Some experimental studies demonstrated that the activity of pyruvate dehydrogenase and the rate of glucose oxidation is low in diabetic animals and type II diabetic patients (Nakai *et al*, 2002; Sugden & Holness, 2002; Huang *et al*, 2003). In addition, the plasma concentration of L-carnitine has been found to be low in diabetic animals and humans (De Palo *et al*, 1981; Tamamogullari *et al*, 1999). Furthermore, continuous infusion of L-carnitine in euglycemic hyperinsulinemic clamp increases insulin sensitivity and glucose oxidation in type II diabetic patients (Capaldo *et al*, 1991; Gaetano *et al*, 1999; Mingron *et al*, 1999). Only one report has been published on the effect of oral L-carnitine in glycemic and lipidemic profile in newly diagnosed patients with type II diabetes mellitus (Derosa *et al*, 2003). The aim of this study was to evaluate for the first time the effect of oral L-carnitine in glycemic and lipidemic profile in long diagnosed patients with type II diabetes mellitus.

Patients and methods

The present study is a double-blind, placebo-controlled, clinical trial over 12 weeks. Patients were recruited from the Diabetic and Metabolic Diseases Center of Medical Shahid Beheshtee University of Tehran, Tehran, Iran. A total of 35 white Caucasian outpatients, 22 men and 13 women, aged

51.3±3.7 y, and with a type II diabetes (according to the criteria of the American Diabetes Association) and a disease duration of 12.3±3.4 y were selected for this study. All patients fulfilled the following criteria:

(1) fasting plasma glucose (FPG) <180 mg/dl and glycosylated hemoglobin (HbA1c) levels <8.0%,
(2) body mass index (BMI) <30 kg/m^2,
(3) serum triglycerides (TG) >150 mg/dl,
(4) no evidence of cardiac or hepatic diseases, and
(5) evidence of diabetic microangiopathic or macroangiopathic complications diagnosed by an expert endocrinologist.

All patients were on oral antidiabetic drugs, glyburide or metformin, and no patients were on insulin or lipid-lowering medication. The study was approved by the Ethics Committee of the Shahid Beheshtee University, and the participants had given written informed consent.

Neuropathy was diagnosed by using questionaires about symptoms of neuropathy, as well as by measurement of nerve conduction velocities by means of a monofilament. Retinopathy was diagnosed on the basis of direct opthalmoloscopy by an ophthalmologist, and nephropathy was diagnosed on the basis of existing microalbuminuria over 30 mg/dl.

The patients were randomized by the use of envelopes containing randomization codes prepared by an independent statistician. One group received treatment with L-carnitine (Sigma–tau, Italy) (3 g/day, divided into three equal doses of 1 g syrup before breakfast, lunch and dinner), and the other group received a corresponding placebo for 12 weeks. Used medication bottles and a supplement using chart were collected at each visit to monitor compliance. The physical activity as well as existing antidiabetic treatment were kept constant during the study.

After an overnight fast of 12 h, blood samples were drawn at baseline, after 6 weeks, and at the end of the study for the evaluation of plasma total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), Apo A-I, Apo B-100, lipoprotein(a) (LP(a)), FPG, and glycosylated hemoglobin (HbA1c). Waist circumferences were measured at the umbilicus and hip circumferences at the level of maximum gluteal protuberances by a tape. The weight of patients was measured by a calibrated scale.

Laboratory assessment

Venous blood samples were taken between 0800 and 0900 hours. Plasma was obtained from the blood samples by adding 1 mg/ml Na_2-EDTA. The blood samples were centrifuged at 3000×g for 15 min at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at −80°C for a period no more than 12 weeks.

All measurements were carried out at the research laboratory of the Endocrine Research Center, Shahid Beheshtee University of Teheran. FPG was measured by the glucose-oxidation method (Pars Azmoon-co, Iran) (intra- and interassay coefficients of variation (CVs) were 3.5 and 3.0%, respectively). The HbA1c level was measured by the ion exchange method (Stand Bio-co USA) (intra- and interassay CVs were 4.2 and 5%, respectively). The TG and TC levels were determined by enzymatic techniques (Pars Azmoon-co, Iran), on an Auto analyzer (RT 1000, USA) (intra- and interassay CVs were 2.0 and 2.6%, respectively). The total and HDL-C levels (after participation with magnesium chloride) were measured by enzymatic techniques (Pars Azmoon-co, Iran) (intra- and interassay CVs were 1.5% and 1.9%, respectively). The LDL-C level was calculated using the Friedewald formula. Apo A-I and Apo B were determined by using the immunoturbidimetric assay (DRG, USA) (intra- and interassay CVs were 3.5% and 4.2%, respectively). LP(a) was measured using the sandwich enzyme-linked immunosorbent assay (ELISA) method (DRG, USA) (inter- and interassay CVs were 5 and 6%, respectively).

Statistical analysis

Statistical analysis of the data was performed using the SPSS statistical software version 11.0. If the distribution was not normal, student's *t*-test or Mann-Whitney *U*-test, was used for comparing the baseline data, comparison of data at 6 and 12 weeks and the changes in biochemical variables across cases and controls. Within-group variations for each variable were tested using repeated measurement analysis of variance or the Friedman test. If there was a main effect, Bonferroni correction was used.

Results

All the 19 patients in the L-carnitine group (12 male and 7 female, mean (s.d.) age 50.5 (4.8) y), and 16 in the placebo group (10 male and 6 female, mean (s.d.) age 52.2 (2.6) y)

Table 1 Baseline demographic characteristics of the patients ($n=35$)

Characteristic	*L-carnitine* (n = *19*)	*Placebo* (n = *16*)
Age (y)	50.5 (4.8)	52.2 (2.6)
Sex (n)		
Men	12	10
Women	7	**6**
Diabetes duration (y)	15.3 (2.3)	14.2 (2.5)
Complication	19	17
Neuropathy (%)	89	82
Retinopathy (%)	32	29
Nephropathy (%)	11	12
Hypoglycemic drugs		
Metformin (%)	80	75
Glyburide (%)	20	25
BMI (kg/m^2)	27.90 (2.0)	28.20 (1.52)
WHR	0.97 (0.17)	0.89 (0.04)

BMI = body mass index; WHR = waist hip ratio (values are expressed as mean (s.d.) unless otherwise denoted).

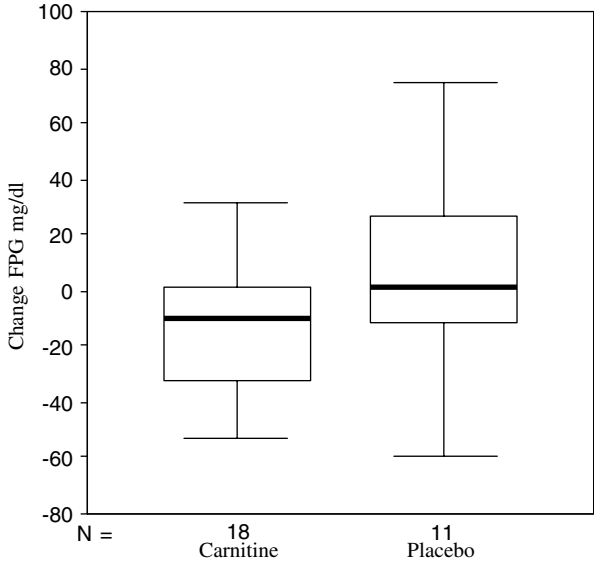

Figure 1 Average change in FPG: mean ± s.d. The differences after 12 weeks is significant ($P = 0.02$).

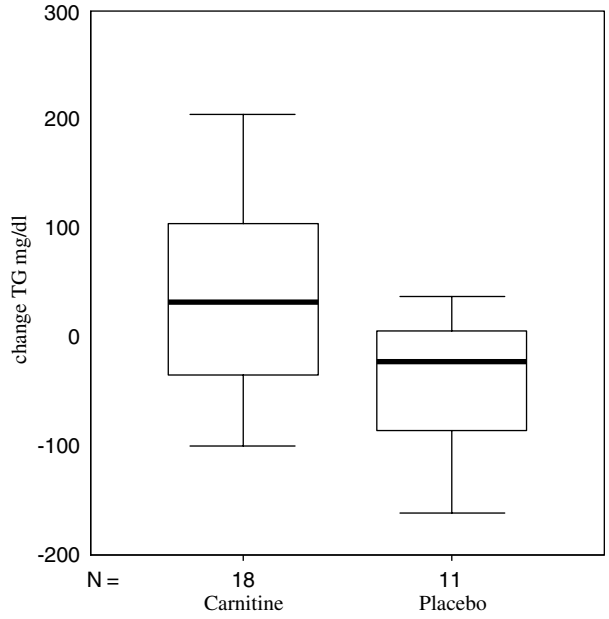

Figure 2 Average change in fasting plasma TG: mean ± s.d. The difference after 12 weeks is significant ($P = 0.02$).

completed the study. Table 1 gives the baseline characteristics of the patients. The baseline characteristics did not differ significantly between the two randomized groups.

After 12 weeks of L-carnitine administration, the concentration of fasting blood glucose had significantly decreased from 143 ± 35 to 130 ± 33 mg/dl ($P = 0.03$). In contrast, in the placebo group, FPG had increased nonsignificantly from 157 ± 27 to 164 ± 47 mg/dl during the study. Consequently, the change in FPG was significantly different between the L-carnitine and the placebo group (−13.50 ± 24.50 mg/dl *vs* 6.46 ± 34.90 mg/dl) ($P = 0.02$) (Figure 1).

The concentration of blood TG after 12 weeks of L-carnitine administration increased significantly from 196 ± 61 to 233 ± 12 mg/dl ($P = 0.05$). This parameter, however, remained significantly unchanged in the placebo group (225 ± 12 *vs* 195 ± 91 mg/dl) during the study. The TG changes were significantly different between the L-carnitine and the placebo group: 37.39 ± 92.24 mg/dl in L-carnitine group *vs* −30.36 ± 90.35 mg/dl in the placebo group ($P = 0.02$) (Figure 2).

After a 12-week administration of L-carnitine, the concentration of fasting serum Apo B100 increased significantly from 98 ± 18 to 108 ± 22 mg/dl ($P = 0.02$), but did not change significantly in the placebo group, 98 ± 23 *vs* 108 ± 24 mg/dl. The changes were significantly different between the L-carnitine and the placebo group (9.22 ± 15.58 *vs* −10.09 ± 15.65 mg/dl in the placebo group ($P = 0.007$) (Figure 3). Moreover, the concentration of fasting serum Apo A-I had significantly increased from 94 ± 20 to 103 ± 23 mg/dl ($P = 0.02$). However, Apo A-1 did not change significantly in the placebo group (from 103 ± 22 to 93 ± 25 mg/dl) during the study. After 12 weeks of L-carnitine

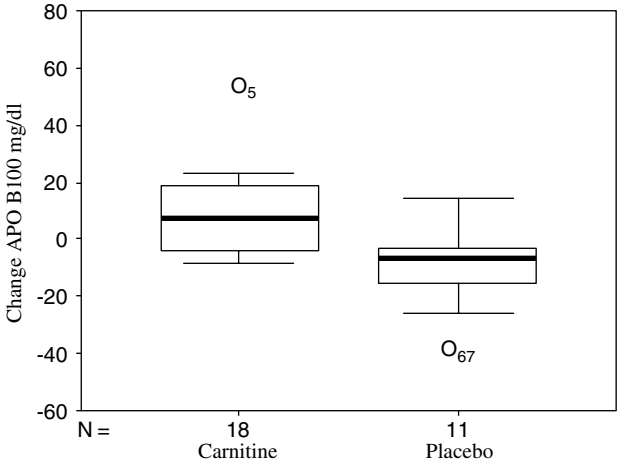

Figure 3 Average change in fasting plasma Apo B100: mean ± s.d. The difference after 12 weeks is significant ($P = 0.02$).

administration, the changes show significant differences between the L-carnitine and the placebo group (8.44 ± 14.22 mg/dl in the L-carnitine group *vs* −9.64 ± 13.54 mg/dl in the placebo group; $P = 0.008$) (Figure 4).

There were no statistically significant changes in HbA1c, LDL-C, HDL-C, LP(a), BMI, WHR in the L-carnitine or the placebo group after 6 and 12 weeks. All differences reached statistical significance only after 12 weeks, and not after 6 weeks. L-Carnitine intake did not lead to any clinically relevant adverse event (Table 2).

Discussion

The present study shows that administration of L-carnitine, added to pre-existent treatment with hypoglycemic drugs (glyburide and metformin), over a period of 12 weeks reduces FPG significantly in type II diabetic patients by about 13%. The magnitude of effect varied among subjects, with some patients having a quite marked decrease (17%) and others having only marginal changes in FPG. Our results are in accordance with those of previous reports of an increase in glucose uptake during hyperinsulinemic euglycemic clamp along with L-carnitine administration (Capaldo *et al*, 1991; Gaetano *et al*, 1999; Mingrone *et al*, 1999).

Derosa *et al*, however, could not find significant effects of oral L-carnitine on FPG in newly diagnosed diabetic patients without diabetic complications (Derosa *et al*, 2003). Tamamogullari *et al* (1999) have indicated that the concentration of L-carnitine is reduced more in neuropathic, retinopathic and nephropathic patients than in diabetic patients without any complication. In our study we investigated, for the first time, the effect of oral L-carnitine on glycemic and lipidemic parameters in patients with long-term type II diabetes and evidence of diabetic complications, as signs of neuropathy, retinopathy and nephropathy. In addition, in our study L-carnitine was administered at a dosage of 3 g, but in Derosa's study L-carnitine was prescribed at 2 g daily (Derosa *et al*, 2003). Rhew and Sachan (1986) reported a dose-dependent effect of L-carnitine in an experimental study.

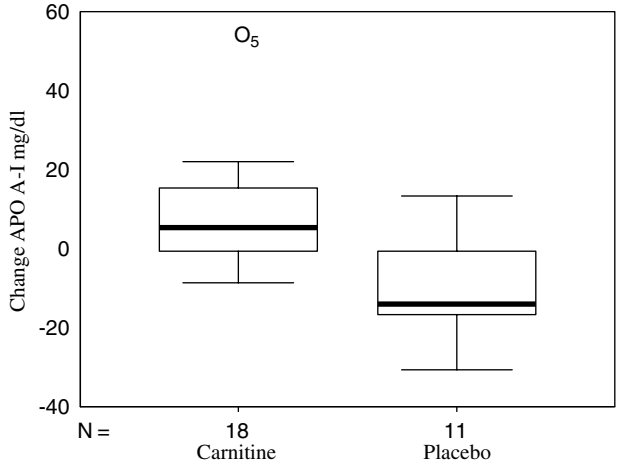

Figure 4 Average change in fasting plasma Apo A-I: mean ± s.d. The difference after 12 weeks is significant ($P = 0.02$).

In our study, L-carnitine increased the TG concentration in diabetic patients; this result is in accordance with one study (Rodrigues *et al*, 1990) and in discordance with another one (Derosa *et al*, 2003). Abdel-aleem *et al* (1997) had shown that the effect of L-carnitine is different in diabetic cells in comparison to nondiabetic cells. Moreover, it did not increase fatty acid oxidation. The following mechanism could explain to some extent the increase of TG in diabetic patients due to L-carnitine. In diabetic cells, carnitine increases the level of cytoplasmic acetyl-CoA due to an activation of pyruvate dehydrogenase (Capaldo *et al*, 1991; Mingron *et al*, 1999). Moreover, acetyl-CoA is the substrate for the synthesis of malonyl-CoA, which is the substrate for fatty acid synthase and a potent inhibitor of carnitine palmitoyltransferase I (CPT I), which thereby inhibits the effect of L-carnitine in intramitochondrial transportation of fatty acids in diabetic patients (Sugden *et al*, 2002). Furthermore in our study, the concentration of Apo B100 was increased significantly in the L-carnitine group. The increase in fatty acids and Apo B100 produces more VLDL in liver and consequently the increase in TG concentration (Davis & Hui, 2001). Furthermore, Gaetano *et al* (1999) reported that L-carnitine inhibits the hypolipidemic effect of insulin in patients with type II diabetes, and L-carnitine in association with insulin infusion increases the concentration of fatty acids in serum.

In our study, the Apo A-I had increased significantly, in accordance with the reports of Stefanutti *et al* (1998). But the HDL-C has not increased concomitantly. The increase in concentration of TG in VLDL remnant, and the increase of

Table 2 Mean (s.d.) changes in variables during treatment with L-carnitine or placebo

	L-Carnitine group			*Placebo group*		
Characteristic	*Baseline*	*6 weeks*	*12 weeks*	*Baseline*	*6 weeks*	*12 weeks*
FPG (mg/dl)	143.94 (35.72)	130.66 (33.38)	130.44 (33.15)†,*	157.54 (27.81)	174.72 (48.54)	164.00 (47.23)
HbA_{1C} (%)	7.33 (1.64)	7.30 (1.44)	7.25 (2.06)	6.90 (2.27)	7.62 (1.47)	7.70 (2.23)
TG (mg/dl)	196.44 (61.62)	203.16 (103.35)	233.83 (116.16)†,*	225.90 (111.90)	204.27 (70.08)	195.54 (91.05)
TC (mg/dl)	179.72 (40.97)	169.50 (37.87)	175.00 (34.51)	203.36 (43.55)	179.27 (29.59)	197.00 (38.51)
HDL-C (mg/dl)	48.77 (16.90)	53.50 (13.45)	40.88 (8.66)	45.90 (13.04)	59.00 (16.16)	40.63 (7.35)
LDL-C (mg/dl)	91.65 (40.26)	76.02 (33.65)	87.34 (38.63)	116.12 (56.96)	86.56 (38.16)	88.10 (28.41)
Apo B (mg/dl)	98.88 (18.99)	95.33 (20.62)	108.11 (22.46)†,*	108.81 (23.63)	94.54 (22.38)	98.72 (24.60)
Apo A-I (mg/dl)	94.61 (20.26)	92.88 (21.16)	103.05 (23.20)†,*	103.00 (22.28)	94.00 (20.91)	93.36 (25.16)
LP(a) (U/dl)	224.05 (341.2)	198.77 (347.55)	205.05 (310.84)	121.81 (103.58)	105.27 (101.22)	105.90 (75.39)

FPG = fasting plasma glucose; HbA_{1C} = glycosylated hemoglobin; TG = triglycerides; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Apo = apolipoprotein; LP(a) = lipoprotein(a).
*$P < 0.05$ *vs* baseline.
$^{\dagger}P < 0.05$ *vs* placebo at 12 weeks.

antiport of TG with cholesterol of HDL at the same time is the probable hypothesis of this phenomenon (Packard & Sheperd, 1995).

The concentration of LP(a) has reduced but not significantly in our study. In the studies of Derosa and Sitori, L-carnitine was able to reduce significantly the concentration of LP(a) in the plasma of diabetic and nondiabetic patients. Perhaps this is the reason why it was not observed (Sirtori *et al*, 2000; Derosa *et al*, 2003). In these studies, patients were selected from high LP(a) individuals, but in our study the patients were low in Lp(a) concentration and there were no significant changes in Lp(a) concentration.

Finally, it is worth mentioning that we did not determine L-carnitine serum levels in the two groups at the beginning and along the study, as tissue levels could play an even more important role, and obviously not measurable. It should be taken into consideration that measuring the L-carnitine concentration in two groups and along the study would make our study more valid and it is the limitation of our report.

In conclusion, in this study we have shown that L-carnitine added to pre-existing antidiabetic therapies significantly lowers fasting plasma glucose levels, but increases fasting triglyceride, in long-term patients with type II diabetes mellitus with evidence of complications.

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