L-Carnitine supplementation reduces oxidized LDL cholesterol in patients with diabetes[1–3]

Mariano Malaguarnera, Marco Vacante, Teresio Avitabile, Marcella Malaguarnera, Lisa Cammalleri, and Massimo Motta

ABSTRACT

Background: Patients with type 2 diabetes are under high oxidative stress, and levels of hyperglycemia correlate strongly with levels of LDL oxidation. Carnitine favorably modulates oxidative stress.

Objective: This objective of this study was to evaluate the efficacy of L-carnitine on the reduction of oxidized LDL cholesterol in patients with type 2 diabetes.

Design: Eighty-one patients with diabetes were randomly assigned to 1 of 2 treatment groups for 3 mo. The 2 groups received either 2 g L-carnitine once daily ($n = 41$) or placebo ($n = 40$). The following variables were assessed at baseline, after washout, and at 1, 2, and 3 mo of treatment: body mass index, fasting plasma glucose, glycosylated hemoglobin, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, apolipoprotein A1, apolipoprotein B-100, oxidized LDL cholesterol, thiobarbituric acid–reactive substances, and conjugated dienes.

Results: At the end of the study period, the L-carnitine-treated patients showed significant improvements compared with the placebo group in the following markers: oxidized LDL levels decreased by 15.1 compared with 3.0 U/L ($P < 0.001$); LDL cholesterol decreased by 0.45 compared with 0.16 mmol/L ($P < 0.05$); triglycerides decreased by 1.02 compared with 0.09 mmol/L ($P < 0.001$); apolipoprotein A1 concentrations decreased by 0.12 compared with 0.03 mg/dL ($P < 0.05$); apolipoprotein B-100 concentrations decreased by 0.13 compared with 0.04 mg/dL ($P < 0.05$); thiobarbituric acid–reactive substance concentrations decreased by 1.92 compared with 0.05 ($P < 0.001$), and conjugated diene concentrations decreased by 0.72 compared with 0.11 in the placebo group ($P < 0.001$).

Conclusion: Our study indicates that oral administration of L-carnitine reduces oxidized LDL cholesterol levels in patients with type 2 diabetes. *Am J Clin Nutr* 2009;89:71–6.

INTRODUCTION

Diabetes mellitus is one of the most common human metabolic diseases, and the underlying derangements in lipid metabolism are important determinants in the course and status of the disease (1, 2). LDL cholesterol is recognized as a major risk of cardiovascular diseases (3) because the oxidation of LDL cholesterol in the plasma or in the subendothelial space of the arterial wall initiates a series of events leading to enhanced uptake of LDL cholesterol by scavenger receptors present on macrophages, smooth muscle cells, or endothelial cells and subsequent foam cell formation (4–6). The oxidative modification of LDL cholesterol greatly increases the conversion of monocytes or macrophages in the arterial wall into cholesterol-laden foam cells, which are an essential component of atherosclerotic plaque (4, 7). An increased susceptibility of LDL cholesterol to oxidation has been observed in patients with angiographically established coronary artery disease and in patients with progression of atherosclerosis who have undergone coronary bypass (8–10).

Oxidative stress and the resulting generation of reactive oxygen species have been implicated as putative mediators of injury in myocardial infarction (11). Oxidation of LDL cholesterol occurs in a wide range of atherosclerosis lesions in human and animal models, and the byproducts generated during this process have numerous negative properties, such as causing cytotoxic damage to vascular walls and inhibiting vasodilatation in response to nitric oxide (12, 13). Patients with diabetes are under high oxidative stress, and hyperglycemia plays an important role in LDL cholesterol oxidation (14, 15). The levels of acute and chronic hyperglycemia correlate strongly with the level of LDL cholesterol oxidation. Furthermore, a close relation between oxidative stress and metabolic control of diabetes has been shown (16–19).

Mitochondria may be an important source of oxidative stress in diabetes (20). L-Carnitine plays an important physiologic role in shuttling the long-chain fatty acids across the inner mitochondrial membrane for β oxidation and ATP production by subsequent oxidative phosphorylation. It also translocates acetyl-CoA into cytoplasm during acetyl-L-carnitine transport out of mitochondria (21). Thus, L-carnitine may be able to restore high-energy phosphate pools in myocardial and other cell types. Studies show a decrease in the concentration of carnitine in blood and tissues in the hyperlipidemic condition (22). Treatment with L-carnitine was reported to normalize the concentrations of carnitine, plasma cholesterol, triglycerides, and thiobarbituric acid–reactive substances (TBARS) in a streptozocin-induced diabetic rat model (23). The studies by Sayed-Ahmed et al (24) further

[1] From the Department of Senescence, Urological and Neurological Sciences (Mariano Malaguarnera, MV, Marcella Malaguarnera, LC, and M Motta), and the Department of Ophthalmology (TA), University of Catania, Catania, Italy.

[2] Supported by a grant from the Ministero dell'Università e Ricerca Scientifica e Tecnologica.

[3] Reprints not available. Address correspondence to M Malaguarnera, Department of Senescence, Urological and Neurological Sciences, University of Catania, Ospedale Cannizzaro, Viale Messina, 829, 95125 Catania, Italy. E-mail: malaguar@unict.it.

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demonstrated that L-carnitine prevented the progression of atherosclerotic lesions in hypercholesterolemic rabbits. L-Carnitine prevented the progression of atherosclerotic lesions because of its antioxidant and lipid-lowering effects. Studies also demonstrated a large decrease in total cholesterol and triglyceride concentrations with L-carnitine supplementation in patients undergoing hemodialysis (25).

In consideration of the pathologic importance of oxidized LDL (Ox-LDL) cholesterol, we examined the effects of L-carnitine treatment on Ox-LDL cholesterol and plasma lipid concentrations in patients with type 2 diabetes (26).

SUBJECTS AND METHODS

Study design

Eighty-one patients with type 2 diabetes (58 men and 23 women) were enrolled in the study. Baseline characteristics of these patients are shown in **Table 1**. Two groups were formed by randomly assigning the study patients. Group 1 received 2 g/d L-carnitine, which was divided into 2 equal doses of one 1-g tablet after breakfast and one 1-g tablet after dinner for 3 mo. Group 2 received a placebo according to the same regimen and for the same duration. Patients were seen by a dietitian every month; at each visit the dietitian provided instructions on dietary intake recording procedures as part of a behavior-modification program, and the patients' resulting food diaries were later used for counseling.

Patient acceptance of the diet planned by the dietitian was good, and compliance with diet was judged to be excellent on the basis of subject feedback and daily records. The following variables were assessed at baseline, after washout, and at 1, 2, and 3 mo of treatment: body mass index (BMI; in kg/m^2), fasting plasma glucose, glycosylated hemoglobin (Hb A_{1c}), total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, apolipoprotein (apo) A1, apo B, Ox-LDL cholesterol, TBARS, and conjugated dienes.

Patients

During the run-in observation period, fasting serum lipid and Ox-LDL cholesterol concentrations were determined at least twice. We enrolled patients with hypercholesterolemia as determined by a National Cholesterol Education Program expert panel (27) and newly diagnosed (≤6 mo) type 2 diabetes, defined according to American Diabetes Association criteria (26), that was managed through dietary restriction alone. A standardized breakfast, lunch, and dinner for each patient were recommended based on a dietitian-prescribed diet. Each patient received 1400–1600 kcal/d of foods with the following components: 55% carbohydrates, 25% proteins, 20% lipids (7% saturated), 105 mg cholesterol, and 36 g fiber. Patients were instructed to maintain the same controlled-energy diet throughout the study. After enrollment, patients provided a medical history and underwent a physical examination that included an electrocardiogram and biochemical/hematologic tests for the measurement of lipids and other components that were part of the safety assessment.

Patients were excluded from this study for the following reasons: *1)* age < 20 or > 70 y; *2)* severe liver or kidney disease, including nephritic syndrome; *3)* pregnancy or lactation; *4)* hypersensitivity to drugs; *5)* history of myocardial infarction or recent or severe episodes of cerebrovascular disease; *6)* hypothyroidism, alcoholism, pancreatitis, multiple myeloma, malignant lymphoma, autoimmune diseases (eg, systemic lupus erythematosus), or Cushing syndrome; *7)* hyperlipidemia induced by drugs such as steroids; and *8)* receiving therapy with statins.

TABLE 1
Baseline characteristics at randomization[1]

	Placebo ($n = 40$)	L-Carnitine ($n = 41$)
Sex (n)		
Men	28	30
Women	12	11
Age (y)	48 ± 11[2]	49 ± 13
BMI (kg/m^2)	27.4 ± 1.8	27.5 ± 1.8
Heart rate (beats/min)	84 ± 12	82 ± 14
SBP (mm Hg)	148.4 ± 16.8	149.1 ± 17.4
DBP (mm Hg)	84.1 ± 10.3	84.6 ± 10.1
Nonsmokers	6	7
Smokers	34	34

[1] DBP, diastolic blood pressure; SBP, systolic blood pressure. There were no significant differences between groups.
[2] Mean ± SD (all such values).

Methods

The study was performed as a 12-wk, double-masked, placebo-controlled group comparison of L-carnitine and placebo. The study protocol was approved by the local research ethics committee (Cannizzaro Hospital, Catania, Italy) and performed in accordance with the Declaration of Helsinki principles (28) and Good Clinical Practice Guidelines. After an initial 4-wk placebo washout, the patients were randomly assigned to 2 groups by selecting envelopes that contained randomization codes prepared by a statistician.

Clinical laboratory tests

Blood samples were obtained after the patients had fasted for 12 h overnight. Venous blood samples were collected from all patients between 0800 and 1000. Plasma was obtained from the blood samples by using EDTA-coated tubes, which were centrifuged at 3000 *g* for 15 min at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at −80°C. The fasting plasma glucose concentrations were assayed using the glucose-oxidase method with intra- and interassay CVs of 0.8% and 2.1%, respectively. The total cholesterol and triglyceride concentrations were measured using fully enzymatic techniques on a clinical chemistry analyzer whose intra- and interassay CVs were 1.1% and 2.2%, respectively, for the total cholesterol measurement and 1.0% and 2.3%, respectively, for the triglyceride measurement. The HDL cholesterol concentration was measured after precipitation of plasma apo B–containing lipoproteins with phosphotungstic acid. The intra- and interassay CVs were 1.0% and 2.0%, respectively. The LDL cholesterol concentration was calculated using the Friedewald formula. The apo A1 and apo B-100 concentrations were measured using immunoturbidimetric assays with the intra- and interassay CVs of 2.8% and 4.7%, respectively. Plasma TBARS and conjugated dienes were also assayed. Ox-LDL cholesterol was measured

by using ELISA in EDTA-coated tubes that contained plasma supplemented with the antioxidants butylhydroxytoluene and diethylenetriaminepentaacetic acid. This Ox-LDL cholesterol ELISA is a capture ELISA that uses the mAb4E6 antibody developed by Holvoet et al (29). The intra- and interassay CVs were 4.9% and 5.2%, respectively. Two control plasma samples with known Ox-LDL cholesterol concentrations that were supplied by the manufacturer (Mercodia, Uppsala, Sweden) were used as internal controls in the analysis.

Efficacy and tolerability assessment

Throughout the randomization phase of the study, thrice-weekly alimentary diary cards were used to collect efficacy data. The primary efficacy measures were changes in triacylglycerols, total cholesterol, HDL cholesterol, and LDL cholesterol. Measurements were made at the beginning and end of the study period.

Statistical analysis

The data were analyzed by using SAS software, version 6.11 (SAS Institute, Cary, NC). Independent *t* tests were performed on all baseline data between groups. Differences in variables at baseline and after treatment were assessed with a repeated-measures analysis of variance that included a time × treatment interaction. Tukey's post hoc tests were used to assess differences between the treatment groups. Differences between means were evaluated by analysis of variance or paired *t* tests where appropriate. Data were further analyzed with a Bonferroni adjusted *t* test for multiple comparisons. The Mann-Whitney *U* test was used to compare nonparametric data. A 2-factor analysis of covariance was used to compare Ox-LDL cholesterol and other plasma variables between the L-carnitine and placebo groups with change in BMI and in glycosylated hemoglobin, which were used as covariates. Simple Pearson's correlations were computed in the total sample of patients with diabetes between initial carnitine intake and the initial values of all dependent variables. To adjust the analyses for confounding variables, simple correlations were repeated by using residual scores for all dependent variables derived from linear regression analysis after adjustment for BMI and Hb A_{1c} as the independent variables. $P < 0.05$ was considered significant. The primary population for statistical analysis was an intention-to-treat population of all randomly assigned subjects.

RESULTS

Enrollment and weight maintenance

No differences were observed between the placebo group and the L-carnitine group in mild hypertension (10% compared with 12%), moderate hypertension (20% compared with 22%), smoking (85% compared with 82%), stage 1 retinopathy (10% compared with 13%), and stage 0 retinopathy (90% compared with 87%) (Table 1). All patients completed the treatment program and maintained the prescribed diet throughout the study.

Effects of carnitine on fasting glucose and glycosylated hemoglobin

No significant decrease was observed in the fasting plasma glucose concentrations in either the L-carnitine- or placebo-treated groups compared with baseline. In the L-carnitine-treated group, however, there was a significant decrease in Hb A_{1c} of 0.6% ($P < 0.001$) after 12 wk treatment. No significant differences were observed between the L-carnitine-treated group and the placebo-treated group in fasting glucose (**Table 2**).

Effects of L-carnitine on blood lipids

Compared with baseline, the decrease of total cholesterol was not significant in the placebo group, whereas in the L-carnitine group it decreased significantly after 12 wk of treatment. Furthermore, in the L-carnitine group, we observed a significant decrease in triglyceride, apo A1, apo B-100, and LDL cholesterol concentrations and a significant increase in HDL cholesterol

TABLE 2
Laboratory parameters in patients treated with placebo and L-carnitine before and after 12 wk of treatment[1]

	Placebo ($n = 40$)		L-Carnitine ($n = 41$)			
	Before treatment	After 12 wk	Before treatment	After 12 wk	P for time[2]	P for group × time[2]
BMI (kg/m^2)	27.0 ± 1.9	26.4 ± 1.5	27.4 ± 1.7	26.8 ± 1.4	NS	NS
Glucose (mmol/L)	7.14 ± 1.40	6.67 ± 1.14	7.04 ± 1.34	6.31 ± 1.18	NS	NS
Hb A_{1c} (%)	7.0 ± 0.7	6.9 ± 0.8	7.3 ± 0.8	6.6 ± 0.8	NS	$P < 0.001$
Total cholesterol (mmol/L)	6.50 ± 0.82	6.20 ± 0.84	6.67 ± 0.86	5.95 ± 0.79	NS	$P < 0.001$
HDL cholesterol (mmol/L)	1.04 ± 0.06	1.08 ± 0.06	1.05 ± 0.05	1.12 ± 0.08	NS	$P < 0.001$
LDL cholesterol (mmol/L)	3.92 ± 0.58	3.76 ± 0.51	3.98 ± 0.56	3.53 ± 0.50	$P < 0.05$	$P < 0.001$
Oxidized LDL cholesterol (U/L)	58.0 ± 10.5	55.0 ± 10.3	58.2 ± 10.4	43.1 ± 10.2	$P < 0.001$	$P < 0.001$
Triglycerides (mmol/L)	3.24 ± 0.37	2.27 ± 0.36	3.31 ± 0.35	2.30 ± 0.31	$P < 0.001$	$P < 0.001$
Apolipoprotein A1 (g/L)	1.41 ± 0.17	1.37 ± 0.16	1.39 ± 0.16	1.27 ± 0.15	$P < 0.05$	$P < 0.05$
Apolipoprotein B-100 (g/L)	1.67 ± 0.16	1.64 ± 0.16	1.69 ± 0.15	1.55 ± 0.14	$P < 0.05$	$P < 0.001$
TBARS (nmol/mL)	8.04 ± 1.22	7.99 ± 1.20	8.10 ± 1.31	6.18 ± 1.27	$P < 0.001$	$P < 0.001$
Conjugates dienes (μmol/mL)	2.44 ± 0.32	2.33 ± 0.36	2.48 ± 0.32	1.76 ± 0.30	$P < 0.001$	$P < 0.001$

[1] All values are means ± SDs. Hb A_{1c}, glycosylated hemoglobin concentration; TBARS, thiobarbituric acid–reactive substances.
[2] ANOVA.

concentrations after 12 wk of treatment compared with baseline. A significant decrease in LDL cholesterol, triglycerides, apo A1, and apo B-100 concentrations in the L-carnitine group compared with the placebo group was observed after 12 wk of treatment. The analysis of covariance showed that these differences were independent of variations in BMI and Hb A_{1c}.

Effects of L-carnitine on oxidative stress

In the L-carnitine group, the Ox-LDL cholesterol, TBARS, and conjugated diene concentrations showed a significant decrease after 12 wk of treatment compared with baseline. In the L-carnitine group compared with placebo, the Ox-LDL cholesterol, TBARS, and conjugated diene concentrations decreased significantly after 12 wk of treatment. The analysis of covariance showed that these differences were independent of variations in BMI and Hb A_{1c}.

Tolerability

Both L-carnitine and placebo were well tolerated in all patients. In the group treated with L-carnitine, 2 patients complained of nausea, 2 complained of slight headache, and 2 complained of abdominal pain. In the placebo group, one patient complained of diarrhea, one complained of nausea, and one complained of headache.

DISCUSSION

L-Carnitine has been reported to have a beneficial effect on several cardiovascular risk parameters, including plasma lipids and lipoprotein(a) (30). Researchers have argued that administration of carnitine may shift the metabolic bias of the liver away from esterification and synthesis of triglycerides toward the formation of acetylcarnitines. This could decrease synthesis of triglycerides and VLDL cholesterol and likely increase mitochondrial β-oxidation of fatty acids. Studies that support this hypothesis indicated that L-carnitine lowers serum cholesterol, triglycerides and free fatty acids (31), and HDL cholesterol (32); yet in other studies carnitine was found to have no effect on triglycerides, total cholesterol, and LDL cholesterol (33, 34). The significant decrease in lipid profile and Ox-LDL cholesterol seen in this study must be interpreted with caution because it is possible that the change in lipid profile is due to the low-fat and high-fiber diet. When we compared the carnitine group with the nontreated placebo group, we observed a significant decrease in LDL cholesterol, Ox-LDL cholesterol, triglycerides, apo A1, apo B-100, TBARS, and conjugated dienes after 12 wk in the carnitine-treated group.

An explanation could be related to the fact that L-carnitine prevents oxidative stress and regulates nitric oxidative stress, nitric oxide, cellular respiration (35), and activity of enzymes involved in defense against oxidative damage (36). L-Carnitine also has a protective effect on the activity of mitochondrial enzyme succinate dehydrogenase and antioxidant enzymes, catalase, and superoxide dismutase, as evidenced in 3-NPA-induced neurotoxicity (37).

In this study L-carnitine treatment reduced Ox-LDL cholesterol concentrations. The underlying mechanism for this action is not yet known but may involve the enhancement of transport of fatty acids by carnitine into mitochondria for energy production. Studies show that the functional consequence of carnitine accretion is the loss of body fat and enhanced fatty acid oxidation (38). Fatty acid mobilization, oxidation, and excretion also were promoted by carnitine supplementation and exercise in women (39). Oxidative stress in patients with diabetes might cause endothelial dysfunction, as shown indirectly by infusion of vitamin C, which improves endothelium-dependent vasodilatation, presumably through its action as an antioxidant (40, 41). Antioxidant properties, especially radical scavenging activities, are important because of the deleterious role of free radicals in biological systems. Excessive formation of free radicals accelerates the oxidation of lipids. These observations support the antioxidant role of carnitine, which is most likely due to stabilization of various membranes, including the mitochondria (42). These observations support the hypothesis that carnitine favorably modulates oxidative stress, most likely by preventing membrane fatty acid peroxidation.

It may be premature to add carnitine to the list of established antioxidants; however, cumulative evidence cannot be ignored entirely (22). Studies showed restoration of the endothelium-dependent relaxation response to acetylcholine and complete normalization of the oxidant-antioxidant state with L-carnitine (43). L-carnitine is also an important cofactor of peroxisomal oxidation, especially for very-long-chain fatty acids, because of the localization of a carnitine acetyltransferase, matrix and cytosol-facing carnitine acetyltransferases, and a carnitine-acetylcarnitine translocase in peroxisomes (44). Carnitine has been shown to inhibit microsomal peroxidation (45), and treatment of aged mice with its acetylated form—acetyl-L-carnitine—ameliorated memory performance and reduced brain lipid hydroperoxide concentrations (46). Previous studies reported that 2 g of L-carnitine reduced plasma lipoprotein(a) without clinically relevant adverse events or negative impact on plasma glucose control (47, 48).

In our previous study we also observed that L-carnitine treatment reduced severity of physical and mental fatigue and increased cognitive functions in elderly subjects and centenarians (49–51). In the current study the decrease in serum concentration of Ox-LDL cholesterol, after a short period of supplementation with L-carnitine, may indicate that this compound lessens oxidative stress in humans. We have observed decreased concentrations of TBARS and conjugated dienes, which are indices of lipid peroxidation, in the circulation of hyperlipidemic patients with diabetes. These decreased concentrations could be attributed to decreased use or increase of antioxidant defense mechanisms. Compositional changes in LDL cholesterol may lead to conformational changes and possibly result in a different exposure of fatty acids to oxygen-free radicals and changes in the rate of lipid peroxidation (52). This argument is supported by the finding that Ox-LDL cholesterol is believed to promote atherogenesis due to increased concentrations of TBARS (53). In diabetes, protein glycation and glucose auto-oxidation may generate free radicals, which in turn catalyze lipid peroxidation and cause pronounced increase in TBARS and conjugated dienes in hyperlipidemic patients with diabetes. Hypertriglyceridemia and hypercholesterolemia were associated with oxidative modification of LDL cholesterol, protein glycation, and glucose auto-oxidation, thus leading to excess production of lipid peroxidation products, which

may cause elevation of oxidative stress in hyperlipidemic patients with diabetes (54). L-Carnitine may provide protective effects on cardiovascular disease by increasing HDL cholesterol, inhibiting the oxidation of LDL cholesterol, and neutralizing the atherogenic effects of Ox-LDL cholesterol.

The authors' responsibilities were as follows—Mariano Malaguarnera: contributed to study design, data analysis, and drafting of the manuscript; LC, MV, and M Motta: contributed to enrollment of patients and data interpretation; Marcella Malaguarnera: helped with statistical analysis and data interpretation; and TA: contributed to evaluation of retinopathy. None of the authors had any relevant personal or financial conflicts of interest.

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