The Effect of L-Carnitine on Plasma Lipoprotein(a) Levels in Hypercholesterolemic Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: A previous study has demonstrated that L-carnitine reduces plasma lipoprotein(a) (Lp[a]) levels in patients with hypercholesterolemia.

Objective: To test a tolerable Lp(a)-reducing agent in diabetic patients, we assessed the effect of a dietary supplementation of L-carnitine on plasma lipid levels, particularly Lp(a), of patients with type 2 diabetes mellitus (DM) and hypercholesterolemia.

Methods: In this 6-month, randomized, double-masked, placebo-controlled clinical trial, patients were enrolled, assessed, and followed up at the Diabetic and Metabolic Diseases Center of the Department of Internal Medicine and Therapeutics at the University of Pavia, Pavia, Italy. All study patients had newly diagnosed type 2 DM that was managed through dietary restriction alone throughout the study, as well as hypercholesterolemia. Patients were randomized to 1 of 2 groups. One group received L-carnitine, one 1-g tablet BID. The other group received a corresponding placebo. We assessed body mass index, fasting plasma glucose, postprandial plasma glucose, glycosylated hemoglobin, fasting plasma insulin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, apolipoprotein (apo) A-I, apo B, and Lp(a) at baseline and at 1, 3, and 6 months of treatment.

Results: This study included 94 patients. The treatment group included 24 men and 22 women (mean [SD] age, 52 [6] years). The placebo group included 23 men and 25 women (mean [SD] age, 50 [7] years). The baseline characteristics of the groups did not differ significantly. The mean (SD) body weight, height,

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and body mass index were 78.2 (5.8) kg, 1.70 (0.04) m, and 27.3 (2.5) kg/m^2, respectively, in the L-carnitine group and 77.6 (6.4) kg, 1.71 (0.05) m, and 26.8 (2.2) kg/m^2, respectively, in the placebo group. In the treatment group, Lp(a) was significantly reduced at 3 and 6 months compared with baseline ($P < 0.05$ and $P < 0.01$, respectively). We observed a significant improvement after 6 months ($P < 0.05$) in the Lp(a) value in patients taking L-carnitine compared with those taking placebo. Between-group differences in other variables did not reach a level of significance at months 3 and 6. No drug-related adverse events were reported or observed.

Conclusion: In this preliminary study, after 3 and 6 months, L-carnitine significantly lowered the plasma Lp(a) level compared with placebo in selected hypercholesterolemic patients with newly diagnosed type 2 DM. (*Clin Ther.* 2003;25:1429–1439)

Key words: L-carnitine, lipoprotein(a), hypercholesterolemia, lipid profile, type 2 diabetes mellitus.

INTRODUCTION

The Third Report of the National Cholesterol Education Program[1] (NCEP) Expert Panel has classified diabetes mellitus (DM) as a myocardial infarction risk equivalent for coronary heart disease events. The same report strongly suggests that all of the associated risk factors of diabetic patients should be reduced to minimize the patients' overall cardiovascular disease (CVD) risk.

Serum lipoprotein(a) (Lp[a]) levels represent either a factor predictive of atherosclerosis or an index of prognosis and severity of atheromatous coronary heart disease.[2,3]

Recent studies have shown an independent association between plasma Lp(a) levels and thoracic aortic atherosclerosis[4] and ischemic stroke.[5] In diabetic patients, plasma Lp(a) levels are often higher than in control subjects[6] and are independently associated with repeat stenosis in femoropopliteal percutaneous transluminal angioplasty[7] and with some typical complications of DM, such as proliferative retinopathy.[8]

A search of PubMed and EMBASE, using terms such as *Lp(a)* and *therapy/treatment,* has shown that during the past 10 years many studies have been carried out to find a therapy to significantly lower Lp(a) levels. In nondiabetic patients at high risk for CVD, aspirin,[9] atorvastatin,[9] and hormone replacement therapy[10] have significantly reduced plasma Lp(a) levels, but only L-carnitine has demonstrated efficacy in selected patients with hypercholesterolemia.[11] In diabetic patients, only niacin administration was tested for its ability to reduce Lp(a), but 22% of those dropped out because of treatment-related adverse events.[12]

To test a tolerable Lp(a)-reducing agent in diabetic patients, we assessed the effect of a dietary supplementation of L-carnitine on plasma lipid levels, particularly Lp(a), of patients with type 2 DM and hypercholesterolemia.

PATIENTS AND METHODS

Patients

Patients with newly diagnosed (within 6 months) type 2 DM according to American Diabetes Association criteria[13] that was managed through dietary restriction alone and with hypercholesterolemia (Lp[a] level, >30 mg/dL) according to the NCEP Expert Panel[1] were enrolled. Patients were recruited from the Diabetic and Metabolic Diseases Center of the Department of Internal Medicine and Therapeutics at the University of Pavia, Pavia, Italy. No patient had a current or previous renal or neoplastic disease. All patients were on a therapeutic DM diet and none were taking hypolipidemic drugs, diuretics, beta-blockers, or thyroxin. All patients received a comprehensive physical examination with an electrocardiogram and a battery of biochemical tests. All patients provided written informed consent.

Methods

The study was performed as a 6-week, double-masked, placebo-controlled, group comparison of L-carnitine and placebo. The study protocol was approved by the local research ethics committee and was performed in accordance with the 1964 Declaration of Helsinki principles and the Good Clinical Practice Guidelines.[14] After an initial 4-week placebo washout period, the patients were randomized, using a drawing of envelopes containing randomization codes prepared by a statistician, to 1 of 2 groups. One group received treatment with L-carnitine (2 g/d, divided into 2 equal doses of one 1-g tablet after breakfast and one 1-g tablet after dinner); the other group, a corresponding placebo for 6 months. Study medication bottles were collected and the tablet counts were recorded at all visits.

Dietitians standardized breakfast, lunch, and dinner, based on a diet prescribed to each patient. Each patient received 1400 to 1600 kcal/d—55% carbohydrates, 25% proteins, 20% lipids ([< 7% saturated], 105 mg cholesterol, 36 g fiber). This controlled-energy diet was continued and the patients were instructed to maintain the same diet throughout the study. Patients were seen by a dietitian every 2 months; at each visit, the dietitian provided instruction on dietary intake–recording procedures as part of a behavior-modification program, and the patients' resulting food diaries were later used for counseling. Furthermore, patients were advised to exercise aerobically by bicycle for at least 30 minutes 3 to 4 days per week throughout the study.

The following variables were assessed at baseline (ie, after washout) and at 1, 3, and 6 months of treatment: body mass index (BMI), fasting plasma glucose (FPG), postprandial plasma glucose (PPG), glycosylated hemoglobin (HbA_{1c}),

fasting plasma insulin (FPI), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), apolipoprotein (apo) A-I, apo B, and Lp(a).

Clinical Laboratory Tests

All plasma chemistry values were determined after the patients had fasted for 12 hours overnight, except for PPG, which was determined 2 hours after the patients had eaten lunch. Venous blood samples were taken from all patients between 9 AM and 10 AM. We used plasma obtained from the blood samples by the addition of Na_2-EDTA, 1 mg/mL and centrifugation at 3000*g* for 15 minutes at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at –80°C for ≤3 months.

The FPG and PPG levels were assayed with the glucose-oxidase method (GOD/PAP®, Roche Diagnostics, Mannheim, Germany), with intra- and interassay coefficients of variation (CVs) of <2.0%.[15] The FPI was assayed with Phadiaseph Insulin Radioimmunoassay® (Pharmacia Corp., Uppsala, Sweden), with use of a second antibody to separate the free and antibody-bound 125 I-insulin, with intra- and interassay CVs: 4.6% and 7.3%, respectively.[16] The HbA_{1c} level was measured with use of high-performance liquid chromatography (Diamat®, Bio-Rad Laboratories Inc., Hercules, California; normal values, 4.2%–6.2%), with intra- and interassay CVs of <2.0%.[17] The TC and TG levels were determined using fully enzymatic techniques[18,19] on a clinical chemistry analyzer (Hitachi 737®, Hitachi High Technologies America, Inc., San Jose, California); the intra- and interassay CVs were 1.0% and 2.1%, respectively, for the TC measurement and 0.9% and 2.4%, respectively, for the TG measurement. The HDL-C level was measured after precipitation of plasma apo B–containing lipoproteins with phosphotungstic acid.[20] The intra- and interassay CVs were 1.0% and 1.9%, respectively. The LDL-C level was calculated using the Friedewald formula.[21] Apo A-I and apo B were measured using immunoturbidimetric assays (Boehringer-Mannheim Corp., Mannheim, Germany); the intra- and interassay CVs were 3.0% to 5.0%, respectively.[22,23] Lp(a) was measured using a sandwich enzyme-linked immunosorbent assay (ELISA) method that is insensitive to the presence of plasminogen, with use of the Macra-Lp(a)® ELISA kit (Strategic Diagnostics, Inc., Newark, Delaware)[24,25]; the intra- and interassay CVs were 5% and 9%, respectively.

All assays were carried out in our department laboratory and the reported CVs were those from the laboratory at which the variables were analyzed.

Statistical Analysis

Statistical analysis of the data was performed using SPSS statistical software version 11.0 (SPSS Inc., Chicago, Illinois); results are expressed as mean (SD). One-

way analysis of variance (ANOVA) was used to compare baseline data. Change was calculated as the value obtained at study end minus the value obtained at baseline. ANOVA also was used to assess the significance within and between groups when a significant value ($P < 0.05$) was found; a 1-sample t test was used to compare values obtained before and after treatment administration, and 2-sample t tests were used for between-group comparisons. Mean changes in Lp(a) in the L-carnitine and placebo groups were analyzed using analysis of covariance (ANCOVA).

RESULTS

A total of 94 patients (46 in the L-carnitine group, 48 in the placebo group) were included (Table I). The L-carnitine group included 24 men and 22 women (mean [SD] age, 52 [6] years). The placebo group included 23 men and 25 women (mean [SD] age, 50 [7] years). The baseline values did not differ significantly between groups. The mean (SD) body weight, height, and BMI were 78.2 (5.8) kg,

Table I. Baseline demographic characteristics of the study patients (N = 94). (Values are expressed as mean [SD] unless otherwise indicated.)

Characteristic	L-Carnitine (n = 46)	Placebo (n = 48)
Age, y	52 (6)	50 (7)
Sex, no. (%)		
Men	24 (52.2)	23 (47.9)
Women	22 (47.8)	25 (52.1)
Race, no. (%)		
White	46 (100)	48 (100)
Diabetes duration, mo	6 (2)	7 (3)
Body weight, kg	78.2 (5.8)	77.6 (6.4)
Height, m	1.70 (0.04)	1.71 (0.05)
BMI, kg/m^2	27.3 (2.5)	26.8 (2.2)
Concomitant disease, no. (%)		
Hypertension	8 (8.5)	8 (8.5)
Concurrent medications, no. (%)		
ACE inhibitors	10 (10.6)	7 (7.4)
Acetylsalicylic acid	8 (8.5)	8 (8.5)
Calcium antagonists	4 (4.3)	8 (8.5)
ARBs	4 (4.3)	4 (4.3)

BMI = body mass index; ACE = angiotensin-converting enzyme; ARBs = angiotensin II–receptor blockers.

1.70 (0.04) m, and 27.3 (2.5) kg/m^2, respectively, in the L-carnitine group and 77.6 (6.4) kg, 1.71 (0.05) m, and 26.8 (2.2) kg/m^2, respectively, in the placebo group. All patients were white; 16 of them (17%) had hypertension and were taking low-dose acetylsalicylic acid and stable antihypertensive therapy (calcium antagonists and/or angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers).

The plasma Lp(a) concentration decreased significantly with L-carnitine after 3 months (difference vs baseline, –3.5% [$P < 0.05$]; difference vs placebo, –6.0% [P = NS]) and after 6 months (difference vs baseline, –20.9% [$P < 0.01$]; difference vs placebo, –16.9% [$P < 0.05$]). With placebo, no significant changes from baseline were observed in plasma Lp(a) levels. Comparisons of the mean changes from baseline at different times observed in each of the 2 groups were performed with ANCOVA, using baseline values as the covariate. Although no between-group differences were reported when data at 1 and 3 months were considered, a statistically significant reduction in Lp(a) was observed at 6 months, after adjustment of data for baseline values ($P < 0.01$). No significant body weight changes were found, and biochemical variables were not significantly modified. BMI did not change significantly in either the L-carnitine or placebo group after 6 months. Compliance, based on counts of the returned tablets, was excellent (>95%) in all patients.

No statistically significant changes in FPG, PPG, HbA_{1c}, or FPI were observed in the L-carnitine or placebo group at 1, 3, or 6 months (Table II). We also found no significant improvements in TC, LDL-C, HDL-C, TG, apo A-I, or apo B in the L-carnitine or placebo group. L-Carnitine intake did not result in any clinically relevant adverse event—only 1 patient (2.2%) experienced a transient slight nausea, which resolved after 3 days of treatment.

DISCUSSION

The effects of L-carnitine on lipoprotein metabolism have been widely investigated in animals[26] and in some specific subcategories of hyperlipidemic patients.[27] In 1978, Maebashi et al[28] reported a 900-mg/d oral supplementation with L-carnitine in subjects affected by type IV hyperlipoproteinemia, and noted a significant decrease in the plasma TG levels without any change in cholesterolemia. This effect has not been widely studied. In patients undergoing hemodialysis, some authors have found that L-carnitine supplementation is associated with a selective reduction in triglyceridemia only in hypertriglyceridemic patients,[29] whereas others have found a significant antihypercholesterolemic effect on TC and LDL-C.[30] Only 1 previous study has assessed the metabolic effect of L-carnitine supplementation on Lp(a). In this study, carried out by Sirtori et al[11] in 2000 in a group of selected patients with high Lp(a) levels, a selective re-

Table II. Mean (SD) changes in variables during treatment with L-carnitine or placebo.

Characteristic	L-Carnitine				Placebo			
	Baseline	Month 1	Month 3	Month 6	Baseline	Month 1	Month 3	Month 6
BMI, kg/m^2	27.3 (2.5)	26.9 (2.1)	26.3 (1.9)	26.2 (2.1)	26.8 (2.2)	26.2 (1.8)	25.8 (1.7)	25.5 (2.0)
FPG, mg/dL	135 (30)	130 (25)	128 (23)	126 (26)	141 (25)	138 (21)	137 (18)	135 (20)
PPG, mg/dL	144 (28)	137 (27)	122.5 (31)	123 (25)	138 (23)	127 (27)	125 (23)	128 (30)
HbA_{1c}, %	7.3 (0.6)	7.2 (0.9)	7.0 (1.1)	6.8 (0.8)	7.1 (0.8)	7.0 (1.0)	6.7 (0.7)	6.5 (1.1)
FPI, μU/mL	14.8 (5.2)	13.4 (7.2)	15.1 (6.4)	14.6 (7.0)	12.4 (6.3)	13.5 (5.5)	12.9 (7.0)	13.0 (6.4)
TC, mg/dL	235 (30)	247 (27)	240 (22)	225 (28)	228 (41)	238 (34)	245 (26)	234 (31)
LDL-C, mg/dL	161 (16)	171 (19)	167.3 (17)	158 (20)	157 (19)	163 (22)	169 (24)	160 (25)
HDL-C, mg/dL	45 (4)	46 (5)	44 (4)	43 (5)	43 (5)	43 (4)	46 (3)	44 (4)
TG, mg/dL	125 (35)	130 (42)	138 (29)	135 (30)	156 (28)	164 (32)	152 (34)	150 (24)
Apo A-I, mg/dL	140 (14)	144 (16)	138 (15)	134 (16)	136 (14)	138 (15)	141 (17)	139 (16)
Apo B, mg/dL	159 (15)	166 (14)	163 (18)	156 (17)	155 (18)	161 (20)	163 (21)	157 (19)
Lp(a), mg/dL	29.6 (18.3)	28.2 (20.1)	26.1 (17.4)*	23.4 (15.3)†‡	27.8 (20.2)	26.4 (18.3)	26.2 (19.8)	26.7 (20.4)

BMI = body mass index; FPG = fasting plasma glucose; PPG = postprandial plasma glucose; HbA_{1c} = glycosylated hemoglobin; FPI = fasting plasma insulin; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; Apo = apolipoprotein; Lp(a) = lipoprotein(a).

*$P < 0.05$ versus baseline.

†$P < 0.01$ versus baseline.

‡$P < 0.05$ versus placebo at 6 months.

duction in plasma Lp(a) level was observed, without significant effects on cholesterolemia or triglyceridemia.

We tested the effect of L-carnitine oral supplementation in diabetic patients, and observed that it did not influence cholesterolemia or triglyceridemia but did significantly reduce the plasma Lp(a) level by 20.9% after 6 months, without clinically relevant adverse events or a negative impact on plasma glucose control. The main difference between our patient sample and that of the Sirtori team[11] is that our study population were all compensated diabetic patients, with mild hypercholesterolemia and borderline high plasma Lp(a) levels. Therefore, the reduction in Lp(a) was less evident in our study than that in the study by Sirtori et al,[11] perhaps because we did not choose selective patients with high Lp(a) levels, as the decrease seems to be related to the baseline Lp(a) levels.

The mechanism whereby L-carnitine can reduce elevated Lp(a) levels is not yet clearly understood. Plasma Lp(a) concentration is strictly under genetic control. It varies widely within different ethnic groups as well as within members of the same family; conversely, the individual range is restricted. All of these facts confirm the importance of genetic control of Lp(a) synthesis, depending on the gene for apolipoprotein(a).[31] With the exception of estrogens, which affect apolipoprotein(a) mRNA expression,[32] drugs that reduce the inflow of fatty acids to the hepatic cells (primarily nicotinic acid and derivatives) are effective treatments to reduce plasma Lp(a) levels.[33] In fact, the effect of high-dose nicotinic acid typically is exerted on patients with elevated Lp(a) levels; that is, those most likely to have increased Lp(a) production.[33] L-carnitine, by stimulation of fatty-acid breakdown at the mitochondrial level, may reduce fatty-acid inflow for Lp(a) production, distinctly lowering the levels of Lp(a) in patients who are presumably affected by excess production of this atherogenic lipoprotein. Even strong inhibition of acylcholesterol acyltransferase seems to be able to significantly reduce plasma Lp(a) levels in experimental models.[34]

The observed result in the diabetic patients in this study could influence the choice of therapy for hypercholesterolemia in diabetic patients, whose plasma L-carnitine level is often reduced. The entity of the reduction seemingly is related to specific DM complications, such as retinopathy, neuropathy, and cardiomyopathy.[35,36] Moreover, L-carnitine may improve blood pressure control in patients already treated with antihypertensive drugs and thus may reduce asthenia, improving the quality of life of these patients.[37]

Because we did not select hyper-Lp(a) diabetic patients, our observed results may underestimate the effects of L-carnitine in this population. Further studies in wider patient samples will help clarify whether the observed results can be extrapolated to the general population.

CONCLUSION

In this preliminary study, after 3 and 6 months, L-carnitine significantly lowered the plasma Lp(a) level compared with placebo in selected hypercholesterolemic patients with newly diagnosed type 2 DM.

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