

The effects of oral L-carnitine treatment on blood lipid metabolism and the body fat content in the diabetic patient

Yiquan Liang,^{1,2} Yanbing Li,¹ Jichuan Shan,¹ Binjie Yu¹ and Zhiqian Ho²

¹ Department of Endocrinology and Metabolism, First Affiliated Hospital, Sun Yat-Sen University of Medical Sciences, Guangzhou, PR China

² Department of Clinical Nutrition, Sun Yat-Sen University of Medical Sciences, Guangzhou, PR China

L-carnitine plays an important role as a factor necessary for the transport of long-chain fatty acids into the mitochondria. A random double blind study was designed to investigate the effects of L-carnitine treatment (12 weeks, 3 g/d) on lipid metabolism and the fat content of the body in the patients with non-insulin-dependent diabetes mellitus. The study details 46 patients, randomly assigned into L-carnitine and placebo groups (23 patients in each group). Patients received either L-carnitine or placebo for 12 weeks. The results revealed that L-carnitine had significant effects on reducing the waist to hip ratio (0.99 ± 0.18 vs 0.95 ± 0.16 , $P < 0.01$), and percentage of body fat ($35.4 \pm 7.1\%$ vs $32.9 \pm 6.9\%$, $P < 0.01$). It also lowered plasma triglyceride (4.0 ± 1.6 mmol/L vs 2.6 ± 1.2 mmol/L, $P < 0.05$), but there were no significant changes in body weight, high density lipoprotein cholesterol, apolipoprotein A or apolipoprotein B. These findings suggest that L-carnitine treatment may promote body fat utilization and result in reduced percentage of body fat and in lower serum triglyceride.

Key words: carnitine, non-insulin-dependent diabetes mellitus, triglycerides, percentage of body fat, fat distribution.

Introduction

L-carnitine is known as a vitamin-like nutrient. One of the main effects of it is the transportation of fatty acid in mitochondria so as may enhance fatty acids metabolism. Some reports indicated that L-carnitine can reduce serum lipids, and improve cardiac function and oppose dysrhythmia.^{1–3} The aim of this study is to evaluate the effects of oral L-carnitine treatment on blood lipid metabolism and the fat content of the body in diabetic patients, which may helpful in the treatment of overweight patients.

Subjects

Fifty outpatients and inpatients with non-insulin-dependent diabetes mellitus (NIDDM, according to 1985 WHO criteria) were selected for this study. All subjects fulfilled the following criteria:

- (1) Fasting plasma glucose levels of <10.0 mmol/L and glycosylated haemoglobin (GHbA_{1c}) levels of $<8.0\%$ on more than two occasions at 4 weekly intervals.
- (2) Body weight $>110\%$ ideal.
- (3) Serum triglyceride (TG) >2.4 mmol/L twice. Other lipid-lowering drugs and thiazides, sex hormones, thyroid reagents and beta-blocking agents were discontinued at least 8 weeks before the study.
- (5) No evidence of cardiac, renal or hepatic disease.
- (6) All subjects volunteered. The study was approved by the Sun Yat-Sen University's equivalent to the ethics committee on the conduct of human research, and a signed consent form was obtained from each subject.

Methods

A random double blind study was designed. The patients

were randomly assigned to either oral L-carnitine or to the placebo group, and were prescribed six tablets (each tablet containing 500 mg L-carnitine; Lonza Company, Berne, Switzerland) or six placebo tablets daily, in three doses for 12 weeks. The diets of each patient, the daily life and activities and basic antidiabetic treatment were kept constant during the study. Fasting blood samples were drawn before the study and at 4 weeks interval during the study for evaluation of serum total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C), high-density lipoprotein cholesterol subtypes HDL₂-C and HDL₃-C (measured using the polyethylene glycol precipitation method), apolipoprotein A₁ (Apo-A₁), apolipoprotein B (Apo-B) (measured using turbidimetry; Beihai Medical Technical Co., Zechiang, PROC), fasting plasma glucose (using the glucose oxidase method) and GHbA_{1c} (using HPLC, Diastat automatic analyzer, Bio-Rad Co., CA, USA). Dual-energy X-ray Absorptiometry (DEXA, Hologic QDR2000, CA, USA) was used to determine the fat content of the body^{4,5} (provided left and right arm, leg trunk and total fat%). Waist and hip circumference were taken with a non-stretch tape. The waist circumference was measured at the umbilicus and the hip was measured at the level of maximum gluteal protuberance. Fasting serum insulin and serum C-peptide levels were measured by radioimmunoassay (Diagnostic Product Co., USA). Insulin tolerance tests were performed to estimate insulin sensitivity. These tests were conducted after an overnight fast; patients

Correspondence address: Dr Zhiqian Ho, Department of Clinical Nutrition, Sun Yat-Sen University of Medical Sciences, 74 Zhong Shan Road, Guangzhou, 510089, PR China.
Tel: + 20 87778223 ext. 2781 Fax: + 20 87765679

were given a bolus of 0.1 unit insulin per kilogram of body weight, blood glucose was measured before and at 5 min interval for the first half-hour after insulin administration,^{6,7} hepatic and renal functions were estimated before and after the study.

Statistical methods

Data were analysed using the Statistical Package for the Social Sciences for Windows, Version 6.0.⁸ The statistical differences between mean values before and after the study were evaluated using the paired samples *t*-test. For comparing more than two groups, one-way ANOVA was used to determine the differences between means.

Results

The comparability of two groups

Fifty patients enrolled in the study; 25 in the L-carnitine treated group (carnitine group) and 25 in the placebo group. Four patients withdrew from the study: one from the carnitine group and one from the placebo group due to side effects (facial flush and skin rash after 5 days and 4 weeks administration, respectively); and one from the carnitine group and one from the placebo group due to relocation. Therefore, a total of 23 patients from each group completed the study. The carnitine group consisted of six males and 17 females (age 59.4 ± 1.7 years), and the placebo group consisted of 10 males and 13 females (age 57.9 ± 2.6 years). The main parameters of both groups before the study were not significantly different (*P*>0.05, Tables 1–3).

The effects of L-carnitine on body weight, waist and hip ratio and plasma glucose concentrations

After 12 weeks of L-carnitine administration, the patients' waist and hip ratios (WHR) were slightly but significantly reduced from 0.99 ± 0.18 to 0.95 ± 0.18. The body weight, body mass index (BMI), fasting plasma glucose and GHbA_{1c} concentrations were unchanged in both active and placebo groups (Table 1).

The effects of L-carnitine on serum lipid concentrations

As shown in Table 2, the TG concentrations in the carnitine group were reduced beginning at 4 weeks and continued to decline, the maximum reduction was obtained after 12 weeks of administration (*P*<0.05). There was a slight reduction but not a statistically significant one in TC concentrations. The values of Apo-A, Apo-B, HDL-C and its subtypes were not influenced. These parameters remained unchanged in the placebo group during the study.

The effects of L-carnitine on the fat content of body

L-carnitine administration significantly reduced the percentage of trunk and total body fat (excluded head). The percentage of fat in the upper arms and lower limbs were not affected. These parameters remained unchanged in the placebo group during the study.

The effects of L-carnitine on the levels of C-peptide and serum insulin and insulin sensitivity

The respective concentration of serum C-peptide and insulin in the carnitine group were 27.9 ± 12.8 mIU/L and 1.3 ± 0.7 nmol/L before treatment and 25.8 ± 14.2 mIU/L and 1.4 ± 0.6 nmol/L after treatment. Corresponding values for the placebo group were 28.3 ± 14.3 mIU/L and 1.4 ± 0.8 nmol/L, and 26.6 ± 13.6 mIU/L and 1.1 ± 0.9 nmol/L. These parameters before and after treatment did not differ in either group. The values of glucose disposal constant K_i (estimated from the slope of the regression line of the logarithm of the blood glucose against time during the insulin tolerance test) before and after treatment showed no difference in either group (1.8 ± 0.9 and 2.3 ± 0.9, and 1.9 ± 0.8 and 2.1 ± 1.0, respectively for the carnitine and placebo groups).

The side effects of the L-carnitine

With the exception of two patients (one from each group) who experienced slight dermoreaction, no patient experienced side effects or discomfort throughout the study. There were no changes in white blood cell count, hepatic function and renal function.

Table 1. The effects of L-carnitine on body weight, waist to hip ratio (WHR) and plasma glucose concentrations (mean ± SD)

	Body weight (kg)		BMI (kg/m ²)		WHR		FPG (mmol/L)		HbA _{1c} (%)	
	Before	After	Before	After	Before	After	Before	After	Before	After
Carnitine	65.7 ± 7.9	63.1 ± 8.4	27.2 ± 3.1	26.1 ± 3.3	0.99 ± 0.18	0.95 ± 0.16*	8.7 ± 3.9	8.1 ± 1.4	8.0 ± 1.7	7.6 ± 1.4
Placebo	66.9 ± 8.8	66.9 ± 8.7	26.9 ± 2.8	26.9 ± 2.9	0.96 ± 0.05	0.98 ± 0.06	8.1 ± 1.5	8.5 ± 1.8	7.8 ± 1.8	7.7 ± 1.3

Compared with the value before carnitine: * *P* < 0.01. WHR, waist:hip ratio; FBG, fasting plasma glucose.

Table 2. The effects of L-carnitine on serum lipid concentrations (mean ± SD)

	Carnitine group (n=23)				Placebo group (n=23)			
	Before	4 weeks	8 weeks	12 weeks	Before	4 weeks	8 weeks	12 weeks
TC (mmol/L)	6.7 ± 1.2	6.6 ± 1.4	6.7 ± 1.4	6.2 ± 1.5	6.4 ± 1.2	6.8 ± 1.3	6.6 ± 1.2	6.3 ± 1.3
TG (mmol/L)	4.0 ± 1.6	3.7 ± 1.5	3.2 ± 1.6*	2.6 ± 1.2*	4.2 ± 2.2	4.4 ± 2.4	4.4 ± 3.2	4.1 ± 2.0
Apo-A ₁ (g/L)	1.29 ± 0.22	1.30 ± 0.16	1.30 ± 0.15	1.36 ± 0.22	1.36 ± 0.29	1.31 ± 0.23	1.40 ± 0.41	1.28 ± 0.25
Apo-B (g/L)	1.20 ± 0.30	1.35 ± 0.26	1.38 ± 0.37	1.31 ± 0.34	1.18 ± 0.43	1.25 ± 0.35	1.39 ± 0.54	1.17 ± 0.46
HDL-C (mmol/L)	1.24 ± 0.46	1.11 ± 0.32	1.21 ± 0.40	1.18 ± 0.40	1.12 ± 0.23	1.09 ± 0.31	1.11 ± 0.36	1.09 ± 0.23
HDL ₂ -C (mmol/L)	0.69 ± 0.37	0.62 ± 0.21	0.64 ± 0.31	0.60 ± 0.22	0.65 ± 0.16	0.56 ± 0.24	0.69 ± 0.14	0.63 ± 0.15
HDL ₃ -C (mmol/L)	0.56 ± 0.24	0.55 ± 0.20	0.61 ± 0.23	0.60 ± 0.21	0.50 ± 0.17	0.50 ± 0.23	0.56 ± 0.18	0.50 ± 0.18

Compared with the value before carnitine: * *P* < 0.05.

Table 3. The effects of L-carnitine on the fat content of body (mean \pm SD)

	Left arm		Right arm		Trunk		Left lower limb		Right lower limb		Total body fat	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Carnitine (<i>n</i> = 23)	51.7 \pm 12.0	50.1 \pm 11.0	48.0 \pm 12.3	48.3 \pm 12.6	33.2 \pm 6.7	31.8 \pm 6.3*	33.0 \pm 8.4	33.2 \pm 7.5	31.6 \pm 8.8	31.8 \pm 7.4	35.4 \pm 7.1	32.9 \pm 6.9*
Placebo (<i>n</i> = 23)	51.5 \pm 10.9	52.8 \pm 10.6	48.0 \pm 12.3	48.3 \pm 12.6	33.6 \pm 6.3	33.8 \pm 6.1	33.1 \pm 6.7	32.8 \pm 6.6	31.8 \pm 6.2	31.9 \pm 6.0	35.8 \pm 6.5	36.3 \pm 6.6

Compared with the value before carnitine: * $P < 0.01$.

Discussion

L-carnitine is necessary for the transfer of long-chain fatty acids into the mitochondrial matrix where they are oxidized.⁹ A lack of sufficient L-carnitine may lead to lipid metabolic abnormalities. Some recent reports have shown that the concentrations of free carnitine in the blood and myocardium of diabetic animals are decreased.¹⁰ The reasons may be excessive degradation of carnitine, a defect in carnitine biosynthesis and secretion by the liver, reduced renal reabsorption and a deficiency of in dietary carnitine.¹⁰ Administration of mega doses L-carnitine may increase blood L-carnitine concentrations and ameliorate hypercholesterolemia and hypertriglyceridemia.¹⁰⁻¹² This study indicated that TG concentrations were reduced from 4.0 ± 1.6 mmol/L to 2.0 ± 1.2 mmol/L ($P < 0.05$) after 12 weeks of L-carnitine administration but the TC concentrations were not significantly decreased, corresponding to the results of Seccombe and Rodrigues in diabetic animals^{10,13} and to the results of Maebashi on patients with hyperlipoproteinemia.¹ Hypertriglyceridemia in NIDDM could mainly be due to increased levels of substrates for triglyceride production, free fatty acid (FFA) and glucose. On the other hand, growing evidence suggests that the failure of insulin to suppress very low density lipoprotein (VLDL) production in the liver may play a central role leading to hypertriglyceridemia in insulin resistant state.^{14,15} Some authors considered the reason for the L-carnitine lowering of triglyceride as being the increased FFA uptake and oxidation which increased the rate of utilization of FFA which results in the reduced incorporation of FFA into TG by synthesis. In either mechanism, inhibition of the synthesis and secretion of triglyceride by liver may result in the L-carnitine lowering of

triglyceride. One report showed that carnitine can correct abnormalities in lipoprotein and apolipoprotein levels.¹⁶ However, our results did not find any effects of carnitine on Apo-A, Apo-B, HDL-C and its subtypes in patients with NIDDM, as reported in rabbits.^{12,17}

Our results after 12 weeks L-carnitine treatments, indicated that the patient's body weight and BMI remained unchanged, but the WHR was significantly reduced from 0.99 ± 0.18 to 0.95 ± 0.18 ($P < 0.01$). Total body fat was significantly decreased ($P < 0.01$) due mainly to the truncal fat (Table 3). It appears that abdominal fat is the dynamic adipose tissue in the body most affected by carnitine. It is interesting that the total fat and waist circumstances were reduced whereas the body weights of patients were unchanged, which suggests that L-carnitine may increase the energy expenditure by increasing adipose tissue oxidation and possibly reducing the utilization of protein and conserving fat-free mass.

Ferrannini *et al.* reported that carnitine can stimulate non-oxidative glucose disposal and improve the effects of insulin.¹⁸ Other studies also noted that oral and injected doses of L-carnitine had plasma glucose lowering effects,^{1,13} but our finding did not show any effects of L-carnitine on fasting plasma glucose, GHbA_{1c}, serum insulin and C-peptide levels. The glucose disposal constant K_i (reflecting insulin sensitivity) showed no change. High-dose carnitine administration (3 g/kg per day i.p.) was reported to reduce plasma glucose and lipid levels in streptozocin-induced diabetic rats.¹⁰ Whether the L-carnitine doses we used were still too low and the parameters we used were not sensitive enough deserve further investigation.

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左旋肉碱对糖尿病病人血脂和体脂分布的影响**摘要**

应用随机双盲方法观察左旋肉碱对NIDDM病人的体重、体脂肪分布和脂代谢的影响。结果显示服用左旋肉碱三个月的治疗组病人的总体脂肪百分数从 $35.4\% \pm 7.1\%$ 降至 $32.9\% \pm 6.9\%$ ($p < 0.01$)；腹围/臀围比从 0.99 ± 0.18 降至 0.95 ± 0.16 ($p < 0.01$)；甘油三酯从 $4.0 \pm 1.6 \text{ mmol/L}$ 降至 $2.6 \pm 1.2 \text{ mmol/L}$ ($p < 0.05$)，但对病人体重、血糖、高密度脂蛋白胆固醇及其亚型和载脂蛋白A1与载脂蛋白B无影响。而对照组未见任何相应改变。提示左旋肉碱有促进NIDDM病人脂肪代谢，增加身体非脂肪组织比例和降低甘油三酯作用。

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