Original Paper

Annals of Nutrition & Metabolism

Ann Nutr Metab 2008;52:335–338
DOI: 10.1159/000151488

Received: January 25, 2008
Accepted after revision: June 5, 2008
Published online: August 19, 2008

Effect of Oral L-Carnitine Administration on Insulin Sensitivity and Lipid Profile in Type 2 Diabetes Mellitus Patients

Manuel González-Ortiz Sandra O. Hernández-González
Eduardo Hernández-Salazar Esperanza Martínez-Abundis

Medical Research Unit in Clinical Epidemiology, Specialties Hospital, Medical Unit of High Specialty, West National Medical Center, Mexican Institute of Social Security, and Cardiovascular Research Unit, Physiology Department, Health Science University Center, University of Guadalajara, Guadalajara, Mexico

Key Words
L-Carnitine · Insulin sensitivity · Lipid profile · Type 2 diabetes

Abstract
Aim: It was the aim of this study to evaluate the effect of oral L-carnitine administration on insulin sensitivity and lipid profile in subjects with type 2 diabetes mellitus. ***Subjects and Methods:*** A randomized, double-blind, placebo-controlled clinical trial was carried out in 12 subjects with type 2 diabetes. Six subjects received L-carnitine 1 g orally 3 times a day before meals for a period of 4 weeks. Six other individuals took a placebo for the same period of time, as the control group. Before and after the intervention, insulin sensitivity and the lipid profile were estimated. To assess insulin sensitivity, the euglycemic-hyperinsulinemic clamp technique was performed. Wilcoxon's signed rank and the Mann-Whitney U test were used for the statistical analyses. ***Results:*** There were no significant differences in basal clinical characteristics between the 2 groups. Insulin sensitivity and the basal lipid profile were similar. There were no significant changes in either group after the intervention in insulin sensitivity (3.2 ± 1.2 vs. 4.5 ± 1.7 mg/kg/min, p = 0.115, and 3.5 ± 0.6 vs. 3.5 ± 0.4 mg/kg/min, p = 0.917, for the placebo and L-carnitine groups, respectively) and in lipid profile. ***Conclusion:*** L-Carnitine orally administered for a period of 4 weeks did not modify insulin sensitivity or the lipid profile.

Introduction

Insulin resistance is a contributing factor to type 2 diabetes; it is associated with a clustering of interrelated plasma lipid abnormalities [1]. Insulin resistance through elevation of plasma free fatty acids (FFAs) contributes to hepatic overproduction of glucose with elevated circulating blood glucose levels [2].

L-Carnitine covers an important role in lipid metabolism, acting as an obligatory cofactor for β-oxidation of FFAs [3]. Several in vitro studies have shown the role of L-carnitine in metabolism, suggesting its influence on FFA oxidation and glucose concentration. Two small controlled short-term trials have examined the beneficial acute effect of intravenous L-carnitine administration on insulin sensitivity in diabetic patients [4, 5]. Unfortunately, there is little information about long-term clinical

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Esperanza Martínez-Abundis, MD, MSc, PhD
Montes Urales 1409, Colonia Independencia
44340 Guadalajara (Mexico)
Tel. +52 33 3826 7022, Fax +52 33 3616 1218
E-Mail esperanzamartinezabundi@yahoo.com

studies for glucose control, using orally administered preparations of L-carnitine; thus, conclusions cannot be made regarding its possible use in diabetes treatment.

The aim of this study was to identify the effect of oral L-carnitine administration on insulin sensitivity and lipid profile in type 2 diabetes mellitus patients.

Subjects and Methods

A randomized, double-blind, placebo-controlled clinical trial was carried out in 12 non-obese [body mass index (BMI) 20–30] adults (30–60 years old) with type 2 diabetes of <5 years, fasting glucose levels between 7 and 10 mmol/l and hemoglobin A1c levels between 7 and 9% without pharmacologic treatment. Subjects were selected from the same neighborhood and socioeconomic status. No participant was excessively sedentary or participated in heavy physical activity. All individuals were non-smokers, their body weight had been stable for at least 3 months before the study with blood pressure <130/80 mm/Hg, and they lacked a personal history of hepatic, renal disease and coronary artery disease. They had not taken any medication known to affect the carbohydrate or lipid metabolism in the previous 6 months. All subjects consumed an isocaloric diet, containing more than 250 g of carbohydrate/day for 3 days before the study, as confirmed by dietary history.

Patients were evaluated before and after the 4-week study period. Tests were performed at 8.00 a.m. after a 10- to 12-hour overnight fasting period. Height and weight were recorded with the individuals wearing light clothing without shoes. Height was measured and rounded off to the nearest centimeter, with the subjects standing. The BMI was calculated as weight (in kilograms) divided by the square of height (in meters). Venous blood was obtained with the subject lying supine in a quiet room. The blood was allowed to clot for 30 min at room temperature and was then centrifuged. The resulting serum was put into an aliquot. The aliquot was immediately used for the measurement of serum glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides.

To assess the insulin sensitivity before and after the pharmacological intervention, an euglycemic-hyperinsulinemic clamp technique was performed. Two venous accesses were established. The first one was placed in a retrograde way in any hand vein through a 23-gauge catheter to obtain blood samples. The hand was wrapped with a thermal pillow until a temperature higher than 40°C was reached to arterialize the blood. The second venous access was established in the contralateral arm with a 20-gauge catheter for infusion. Insulin (Humulin R; Eli Lilly Co., Mexico) was given as a primed continuous infusion targeted to produce plasma insulin levels of approximately 600 pmol/l. Thereafter, the insulin infusion rate was fixed at 284 pmol/l/m^2/min. The blood glucose level was constant (about 5 mmol/l, with a coefficient of variation of <5%) throughout the study (120 min) by infusing 10% glucose at various rates according to blood glucose measurements performed at 5-min intervals. At the end of the clamp technique, the 10% glucose infusion was maintained for another 30 min, as a precaution to avoid hypoglycemia. Total glucose metabolism was used to evaluate the insulin sensitivity.

Pharmacologic Administration

After randomization, L-carnitine base 1 g (Procesos y Reactivos Químicos, S.A. de C.V. México) or placebo, each in a solution mixed with methylcellulose and sucralose, was administered orally 3 times per day before meals for 4 weeks.

The serum glucose was determined by the glucose-oxidase technique (Beckman Instruments, Inc., Brea, Calif., USA) with an intra- and interassay coefficient of variation of <1%. Serum lipid levels (total cholesterol, HDL cholesterol and triglycerides) were measured by enzymatic methods. In particular, HDL cholesterol was assessed after selective precipitation of non-HDL fractions. Determinations were performed with commercially available equipment (Ortho-Clinical Diagnostics, Inc., Rochester, N.Y., USA) with an intra- and interassay coefficient of variation of <3%.

Low-density lipoprotein cholesterol was estimated by the Friedewald formula (low-density lipoprotein cholesterol = total cholesterol – HDL cholesterol – tryglicerides/5). Very low-density lipoprotein was calculated as triglycerides/5.

Statistical Analyses

The sample size was calculated using a clinical trial formula [6] with a confidence level of 95%, power of 80%, a standard deviation of glucose metabolized of 1.2 mg/kg/min [7, 8] and an expected difference of at least 1.9 mg/kg/min of glucose metabolized among groups. Values were converted to SI units and are presented as mean ± standard deviation. The intra- and intergroup differences were tested by the Wilcoxon's signed rank and the Mann-Whitney U test, respectively.

Ethic Considerations

The study protocol was reviewed and approved by the hospital-based ethics committee, and a written informed consent was obtained from all volunteers.

Results

All 12 subjects who were eligible after screening completed 4 weeks of pharmacologic intervention. Both placebo and L-carnitine groups consisted of 3 females and 3 males. There were no significant differences in the ages between the groups (42.6 ± 9.2 vs. 44.1 ± 7.3 years, p = 0.485, for the placebo and L-carnitine group, respectively). The BMI was not modified by the intervention (27.8 ± 2.7 vs. 27.5 ± 2.7, p = 0.138, and 27.2 ± 2.7 vs. 26.9 ± 2.4, p = 0.500, for the placebo and L-carnitine group, respectively).

There were no significant differences in metabolic characteristics between the 2 groups at baseline or after placebo or L-carnitine administration (table 1).

Hyperglycemic events were not observed. No additional adverse events were presented that could be related to drug administration.

Table 1. Metabolic characteristics of the studied groups before and after the intervention

	Placebo			L-Carnitine		
	basal	4 weeks	p	basal	4 weeks	p
Glucose, mmol/l	6.7 ± 0.7	6.3 ± 1.0	0.752	6.6 ± 0.9	6.5 ± 0.8	0.674
Total cholesterol, mmol/l	4.3 ± 1.1	4.8 ± 1.4	0.206	4.9 ± 1.1	4.7 ± 0.8	0.345
Triglycerides, mmol/l	1.7 ± 1.0	1.7 ± 0.8	0.144	1.4 ± 0.9	1.6 ± 1.0	0.715
HDL cholesterol, mmol/l	0.9 ± 0.3	1.0 ± 0.1	0.345	0.9 ± 0.2	0.8 ± 0.2	0.785
LDL cholesterol, mmol/l	2.7 ± 0.9	3.0 ± 1.1	0.116	3.0 ± 1.0	2.6 ± 0.6	0.345
VLDL, mmol/l	0.6 ± 0.3	0.7 ± 0.3	0.917	0.9 ± 0.3	1.0 ± 0.2	0.832
A1C, %	7.2 ± 1.6	6.5 ± 0.8	0.116	6.7 ± 0.8	6.3 ± 0.7	0.248
M, mg/kg/min	3.2 ± 1.2	4.5 ± 1.7	0.115	3.5 ± 0.6	3.5 ± 0.4	0.917

LDL = Low-density lipoprotein; VLDL = very low-density lipoprotein; A1C = hemoglobin A1c; M = glucose metabolized.

Discussion

The role of nutritional and botanical substances in diabetes treatment has not been completely studied; available information suggests that some of them are capable of decreasing insulin resistance. Amino acids, including carnitine, could decrease the insulin resistance [9], although other publications do not support this traditional concept [10].

Two possible mechanisms are involved in the metabolic effect of L-carnitine and its derivatives: a regulation of acetyl and acyl cellular trafficking for correctly meeting the energy demand and a control in the synthesis of glycolytic and gluconeogenic key enzymes [11].

It has been reported that an acute state of hypercarnitinemia stimulates nonoxidative glucose disposal in healthy volunteers [12] as well as in type 2 diabetic patients [5]. Glucose disposal is significantly associated with serum lipids and FFA concentrations. L-Carnitine inhibits the hypolipidemic effect of insulin in patients with type 2 diabetes and, in association with an infusion of insulin, increases the FFA concentrations [13]. The effect of L-carnitine on oxidative metabolism does not seem to depend on the alteration of the stability of mRNA; the intracellular patterns of transcriptional regulation in carnitine acetyltransferase and in carnitine palmitoyltransferases (CPT1A and CPT2) are different and dependent on the presence or absence of carnitine [14]. L-Carnitine, in similar doses to those used in our study, has showed reducing glucose and increasing triglycerides [15].

In this study, there were no changes in lipids or in insulin sensitivity due to L-carnitine administration. There are some possible explanations for our results. The intracellular homeostasis of carnitine is mainly controlled by the organic cation transporter OCTN2, which operates on the intestinal absorption and renal reabsorption of L-carnitine; its expression is reduced by several factors, including aging, and this could affect the carnitine acetyltransferase, CPT1A and CPT2 actions with a consequent effect on fatty acid oxidation and lipid concentrations [16]. The lipid profile was not modified with L-carnitine administration; therefore, there was no effect on insulin sensitivity. Indications to follow a specific diet and a physical activity were probably not carried out for all patients in the same way.

We consider it necessary to design more investigations with different doses of L-carnitine and with a longer intervention to reach strong statements.

In conclusion, the administration of L-carnitine 1 g orally 3 times a day before meals for a period of 4 weeks was unable to improve insulin sensitivity and to modify a lipid profile in type 2 diabetes patients.

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