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THE EFFECT OF L-CARNITINE ON INSULIN RESISTANCE IN HEMODIALYSED PATIENTS WITH CHRONIC RENAL FAILURE

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ABSTRACT: We investigated the effect of L-carnitine in seven patients, four female and three male (mean age 44.4 ± 6.0 years) with chronic renal failure. Six patients, four female and two male (mean age 49.3 ± 2.2 years) with chronic renal failure were given a placebo (0.9% sodium chloride) as control. After the basal data were obtained, patients received a single intravenous dose of L-carnitine (1 g) or placebo and two hours later insulin sensitivity was studied by the intravenous insulin tolerance test. No change was observed in biochemical data and K_{itt} values in the placebo group. K_{itt} increased significantly with carnitine (from 2.99 ± 0.3 to 3.54 ± 0.2%/min, $p < 0.03$) compared to the control group ($p < 0.02$). This result suggests that L-carnitine may improve the insulin resistance common among uremic patients.

KEY WORDS: *Chronic renal failure, Insulin resistance, L-carnitine*

INTRODUCTION

Almost all patients with chronic renal failure have reduced tissue sensitivity to the hypoglycemic action of insulin. Nutritional, metabolic and cardiovascular complications of renal diseases may be related to this (1). The pathogenesis of insulin resistance and glucose intolerance in uremia is still not known. Possible pathogenic factors include uremic toxins (2), poor exercise tolerance (3), metabolic acidosis (4), vitamin D deficiency and/or secondary heperparathyroidism (5-7) and anemia (8). Insulin resistance associated with renal failure results from post-receptor defects in insulin action in muscle, adipose, and liver tissues. These defects are primarily restricted to glucose uptake and metabolism by these insulin-sensitive tissues (9). Generation of the intracellular mediators that stimulate pyruvate dehydrogenase for insulin action may be defective in uremia (10).

Carnitine is an essential co-factor for the transport of long-chain fatty acids into mitochondria for oxidation. Carnitine depletion results in depressed mitochondrial oxidation of fatty acids and in cytoplasmic accumulation of lipids, which may impair liver, muscle and myocardial functions (11). The plasma concentration of total carnitine is normal of high in dialysis patients. However, the free carnitine concentration is subnormal whereas the concentration of carnitine esters (acylcarnitine) is markedly elevated (12, 13). Therefore, in order to see whether the low free carnitine concentration was related to insulin resistance, we tested the insulin sensitivity of hemodialysis patients by the insulin tolerance test before and after an intravenous dose of L-carnitine.

MATERIAL AND METHODS

We investigated the effect of i.v. L-carnitine (LC) on insulin resistance in seven patients, four female and three male, with chronic renal failure. The results were compared with six patients matched for sex, age and body mass index, four female and two male, mean age with chronic renal failure who received placebo (P) (0.9% sodium chloride). The main clinical characteristics of the LC and P groups are shown in Table I. All patients were on regular hemodialysis three times a week. None of the patients was diabetic or glucose-intolerant and none of them had a family history of diabetes mellitus. They were not receiving any drug that could effect the glucose insulin metabolism. Informed consent was obtained from each subject before the study. The Ethical Committee of Firat University Hospital approved this study design.

All studies started at 8.30 a.m. after an overnight fast, just before hemodialysis. An intravenous cannula was inserted into the antecubital vein and kept patent with 0.9% saline solution. After a basal insulin tolerance test, LC and P groups received a single i.v. dose of L-carnitine (1 g) or placebo (0.9% sodium chloride). Two hours later basal samples were taken, and a bolus of 0.1 units/kg regular insulin was injected i.v. Blood samples were then obtained at 3, 6, 9, 12, 15, 20 and 30 minutes for the measurement of blood glucose levels. Glucose was infused after 30 minutes to avoid hypoglycemic complications.

Blood was rapidly centrifuged and glucose was immediately measured by the oxidase method. The remaining plasma was stored at -20 °C for insulin and C-peptide assays. Serum levels of C-peptide (DPC, Los Angeles, USA) were measured by a chemiluminescent enzyme immunoassay. The intra- and inter-assay coefficients of variation of the C-peptide were 7.5% and 5.9% respectively and the sensitivity of the assay was 0.3 ng/ml. Serum levels of insulin (Icn Micromedic Systems) were measured by radioimmunoassay and its intra- and inter-assay coefficients of variation were 4.21% and 8.47% respectively, the senstivity of the assay being 1.0 μIU/ml.

The rate constant for plasma glucose disappearance (K_{itt}) was calculated from the formula $0.693/t_{1/2}$. The plasma glucose $t_{1/2}$ was calculated from the slope of the least square analysis of the plasma glucose concentrations from 3-15 min after intravenous insulin, when the concentration declined linearly (14, 15). Differences in means for the LC and P

Table I - Main clinical characteristics of L-carnitine and placebo groups

	L-Carnitine (n=7)	Placebo (n=6)
Age (years, mean ± SE, range)	44.4 ± 6.0 (21-66)	49.3 ± 2.2 (25-61)
Female/male	4/3	4/2
BMI (kg/m²)	23.9 ± 3.9	24.5 ± 2.2
Dialysis duration (months)	38.4 ± 9.5 (14-96)	40.0 ± 11.8 (10-90)

Table II - Biochemical data and K_{itt} before and after L-carnitine and placebo

	Placebo (n=6)			L-Carnitine (n=7)		
	Before	After	p	Before	After	p
Fasting glucose (mmol/L)	5.13 ± 0.2	4.94 ± 0.4	NS	5.19 ± 0.2	4.84 ± 0.1	NS
Cholesterol (mmol/L)	4.37 ± 0.4	4.21 ± 0.4	NS	4.37 ± 0.6	4.87 ± 0.5	NS
Triglycerides (g/L)	1.66 ± 0.3	1.64 ± 0.2	NS	1.87 ± 0.7	1.91 ± 0.7	NS
Calcium (mmol/L)	2.00 ± 0.1	1.98 ± 0.2	NS	1.94 ± 0.1	1.97 ± 0.1	NS
Phosphorus (mmol/L)	1.92 ± 0.2	1.89 ± 0.3	NS	1.88 ± 0.1	1.94 ± 0.4	NS
C-peptide (µg/L)	4.90 ± 0.9	5.01 ± 0.1	NS	5.98 ± 0.9	7.35 ± 2.3	NS
Insulin (µmol/L)	36.9 ± 7.6	38.1 ± 8.2	NS	40.60 ± 5.4	32.80 ± 4.0	NS
K_{itt} (%/min)	3.30 ± 0.4	3.37 ± 0.4	NS	2.99 ± 0.3	3.54 ± 0.2*	< 0.03

K_{itt}: rate constant for plasma glucose disappearance
**: $p < 0.02$ compared with placebo*

groups were tested by the Mann-Whitney U test. Wilcoxon's Rank Sum test was used to analyze differences before and after LC or P. All data are given as meant ± SEM. $P < 0.05$ was considered significant.

Results

All the biochemical data and K_{itt} values (coefficient of variation, 22.0 ± 3.7%) before and after LC or 0.9% sodium chloride injections are summarized in Table II. No changes were observed in the placebo group. K_{itt} increased significantly in the LC group, more than in the placebo group ($p < 0.02$). Despite normal glucose levels, the basal insulin levels in the uremic patients were markedly elevated (40.60 ± 5.4 in LC and 36.9 ± 7.6 µmol/L in P, normal range 3-15 µmol/L). The insulin concentration decreased insignificantly and the C-peptide concentration increased insignificantly after LC. Fasting glucose, urea, creatinine, uric acid, cholesterol, triglycerides, calcium and phosphorus in the LC group remained unchanged.

Discussion

This study found that L-carnitine may improve insulin resistance in patients with chronic renal failure. We previously demonstrated that uremic patients were insulin-resistant and hyperinsulinemic (7). The fatty acid metabolism is impaired in uremia and may lead to the production of large numbers of incompletely metabolized acyl moieties. Normally these are taken up by carnitine and the resulting acylcarnitine is removed by the kidneys. With the impairment of renal function, short and long chain acylcarnitines accumulate in plasma (16). Acyl moieties are harmful to cellular metabolism because they inhibit several key enzymes including pyruvate dehydrogenase (17). Moreover, during hemodialysis fatty acids rise in plasma, resulting in an increased influx of fatty acids into tissues (18, 19).

Free fatty acids induce insulin resistance by inhibiting muscle glycogen synthesis and glucose oxidation (20, 21). Maeda et al observed that carnitine treatment was associated with a lower free fatty acid concentration during hemodialysis and concluded this was the result of increased fatty acid oxidation (22). We suggest that administering LC may lessen insulin resistance by improving the function of pyruvate dehydrogenase, by scavenging these acyl moieties and/or by lower the free fatty acid concentration.

Basal insulin levels in the uremic patients were markedly elevated. This may be a compensatory mechanism to overcome peripheral insulin resistance (23). After LC plasma insulin decreased slightly, possibly because of an increase in the hepatic clearance of insulin (24), and also because of the lower insulin requirement as the response to insulin improves with LC.

Basal C-peptide levels in uremic patients were also high, increased slightly after LC, in contrast to insulin. Insulin is degraded in the kidney, liver and peripheral tissues, but C-peptide is only broken down in the kidney. We concluded that serum levels of the C-peptide, which is released equimolarly with insulin, may increase because of decreased clearance of C-peptide.

L-carnitine appears to improve insulin resistance in patients with chronic renal failure, possibly by regulating the cell energy metabolism or reducing free fatty acids and abnormalities in the carnitine metabolism. However, the sample size in this study is too small to permit any firm conclusion about LC's effects on insulin resistance.

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