Original Paper

L-Carnitine Improves Glucose Disposal in Type 2 Diabetic Patients

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Objective: Aim of the present study is to evaluate the effects of L-carnitine on insulin-mediated glucose uptake and oxidation in type II diabetic patients and compare the results with those in healthy controls.

Design: Fifteen type II diabetic patients and 20 healthy volunteers underwent a short-term (2 hours) euglycemic hyperinsulinemic clamp with simultaneous constant infusion of L-carnitine (0.28 μmole/kg bw/minute) or saline solution. Respiratory gas exchange was measured by an open-circuit ventilated hood system. Plasma glucose, insulin, non-esterified fatty acids (NEFA) and lactate levels were analyzed. Nitrogen urinary excretion was calculated to evaluate protein oxidation.

Results: Whole body glucose uptake was significantly ($p<0.001$) higher with L-carnitine than with saline solution in the two groups investigated (48.66 ± 4.73 without carnitine and 52.75 ± 5.19 μmoles/kg_{ffm}/minute with carnitine in healthy controls, and 35.90 ± 5.00 vs. 38.90 ± 5.16 μmoles/kg_{ffm}/minute in diabetic patients). Glucose oxidation significantly increased only in the diabetic group (17.61 ± 3.33 vs. 16.45 ± 2.95 μmoles/kg_{ffm}/minute, $p<0.001$). On the contrary, glucose storage increased in both groups (controls: 26.36 ± 3.25 vs. 22.79 ± 3.46 μmoles/kg_{ffm}/minute, $p<0.001$; diabetics: 21.28 ± 3.18 vs. 19.66 ± 3.04 μmoles/kg_{ffm}/minute, $p<0.001$). In type II diabetic patients, plasma lactate significantly decreased during L-carnitine infusion compared to saline, going from the basal period to the end-clamp period (0.028 ± 0.0191 without carnitine and 0.0759 ± 0.0329 with carnitine, $p<0.0003$).

Conclusions: L-carnitine constant infusion improves insulin sensitivity in insulin resistant diabetic patients; a significant effect on whole body insulin-mediated glucose uptake is also observed in normal subjects. In diabetics, glucose, taken up by the tissues, appears to be promptly utilized as fuel since glucose oxidation is increased during L-carnitine administration. The significantly reduced plasma levels of lactate suggest that this effect might be exerted through the activation of pyruvate dehydrogenase, whose activity is depressed in the insulin resistant status.

INTRODUCTION

There is experimental evidence that L-carnitine (LC) stimulates the activity of the pyruvate dehydrogenase (PDH) complex by decreasing the intramitochondrial acetyl-CoA/CoA ratio through the trapping of acetyl groups [1]. The simultaneous reduction of acetyl-CoA levels in the cytosol further contributes to activate the glycolytic pathway [2].

Broderick et al [3] showed that glucose oxidation rates in control hearts were markedly decreased if fatty acids were present in the perfusate. In hearts containing raised concentrations of carnitine, there was a significant increase in glucose oxidation accompanied by a parallel decrease in palmitate oxidation. The effects of carnitine loading on glucose oxidation did not occur in hearts perfused in the absence of fatty acids suggesting that L-carnitine might act as a switcher (or a modulator) of fuel substrate utilization in the cells.

Wall and Lopaschuk [4] demonstrated that stimulation of glucose oxidation by L-carnitine can improve function in the diabetic heart and McGarry et al [5] showed that LC increases both CoA levels and reduces acetyl-CoA levels, thus resulting in a 10- to 20-fold decrease in the acetyl-CoA/CoA ratio.

It has been reported [6], using the clamp technique, that L-carnitine administration results in a stable increase (around

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17% above the basal value) of whole body glucose disposal in healthy young volunteers. In this study, only non-oxidative glucose disposal appeared to be enhanced by hypercarnitinemia, while net oxidation of glucose was apparently unaffected.

Capaldo et al [7] investigated the effects of LC on insulin sensitivity in type 2 diabetic patients by euglycemic-hyperinsulinemic clamp. They found that whole body glucose utilization was significantly higher when LC was infused. Unfortunately, they did not perform indirect calorimetric measurements, so that no information on glucose oxidation under LC infusion in type 2 diabetic patients is available.

Since few drugs that improve insulin resistance (like metformin [8,9] and troglitazone [10,11], are therapeutically available, it is relevant to study the possible effect of LC on increasing glucose uptake and oxidation in type 2 diabetes who demonstrate an insulin resistant condition. In the present study we investigated the effect of I.V. continuous infusion of L-carnitine on glucose disposal evaluated with the euglycemic hyperinsulinemic clamp (EHC) associated with indirect calorimetric measurements. Plasma free fatty acids and lactate levels were also assayed.

PATIENTS AND METHODS

Subjects

The study group consisted of 15 non-obese healthy volunteers and 20 type 2 diabetic patients. The anthropometric characteristics of the studied subjects are reported in Table 1.

Body weight was measured to the nearest 0.1 kg by a beam scale. Body composition was estimated on the basis of the total body water (TBW) measured by isotopic dilution [12]. Briefly, 80 μCi of tritiated water (100 mCi/ml) in 5 ml of saline solution were administered as an intravenous bolus injection. The dpm were counted in duplicate on 0.5 ml of plasma using a Beta-Scintillation Counter (Canberra-Packard, Model 1600TR, Canberra, CT, USA) and were plotted against time. To compute the apparent volume of distribution of the labeled water (equal to the TBW), the total amount of tritiated water injected as a bolus was divided by the average concentration of labeled water at the steady state. FFM was calculated as TBW divided by 0.73. Subjects were clinically euthyroid, had no stigmata of renal, cardiac or hepatic dysfunction and were not taking any drugs other than those for diabetes.

Table 1. Anthropometric Characteristics of the Subjects and Baseline Values by Group

	Control subjects	Type 2 diabetics	p
Number of subjects	20	15	
Sex	11M/9F	8M/7F	
Age (years)	47.3±8.0	48.0±5.9	NS
Weight (kg)	67.2±8.2	70.6±6.7	NS
Height (cm)	166.4±6.6	165.4±4.9	NS
Fat-free mass (kg)	48.1±4.3	45.8±5.1	NS
Fat mass (kg)	19.1±4.6	24.9±5.5	<0.01
Basal plasma glucose (mmol/l)	4.4±0.7	5.7±0.8	<0.001
Basal plasma insulin (pM)	38.7±13.6	117.1±27.3	<0.0001
Basal plasma lactate (mM)	1.70±0.37	2.50±0.50	NS
Basal plasma NEFA (mM)	794.4±100.3	833.5±116.7	<0.001
Resting energy expenditure (kJ/24 hour)	6925±766	7038±810	NS
Fasting respiratory quotient (#)	0.86±0.04	0.86±.003	NS

Data reported as mean±SD.

Type II diabetic patients (HbA1c average value of the last month=7.5±0.6%) were treated with a therapeutic dose of three tablets a day of oral hypoglycemic agents (OHA) (glibenclamide 2.5 mg+metformin 500 mg) plus a bedtime dose (from 15 to 20 UI) of human intermediate action insulin (ProtaphaneHM, Novo Nordisk, Denmark). One week before the experimental sessions OHA were suspended and blood glucose was controlled with rapid action insulin (Actrapid HM, Novo Nordisk, Denmark) administration before the main meals.

All subjects consumed a weight-maintaining diet consisting of at least 250 g carbohydrates/day for 1 week before the study.

The study was conducted according to the Declaration of Helsinki and according to the guidelines of the Institutional Review Board of the School of Medicine of the Catholic University in Rome, Italy. Written informed consents were obtained from all subjects before the experiment.

Experimental Protocol

All subjects were admitted to the Department of Metabolic Diseases of the Catholic University in Rome at 6.00 p.m. of the day before the study. At 7:00 a.m. on the following morning, indirect calorimetric monitoring was started; the infusion catheter was inserted into an antecubital vein; the sampling catheter was introduced in the contralateral dorsal hand vein and this hand was kept in a heated box (60°C) to obtain arterialized blood. The glycemia of diabetic patients was maintained below 100 mg/dl by small bolus doses of short-acting human insulin (Actrapid HM, Novo Nordisk, Denmark) until the beginning of the study. At 9.00 a.m., after 12 to 14 hour overnight fast, the euglycemic hyperinsulinemic glucose clamp was performed as described by De Fronzo et al [13]. A priming dose of short-acting human insulin was given during the initial 10 minutes in a logarithmically decreasing way, in order to acutely raise the serum insulin to the desired concentration. Constant insulin state was then maintained constant with a continuous infusion of insulin at an infusion rate of 40 mU/m^2/minute for 110 minutes. During the clamp, the glucose level was monitored every 5 minutes and the infusion rate of a 20% glucose solution was adjusted following the algorithm detailed by De Fronzo [13]. L-carnitine (Sigma Tau S.P.A., Rome, Italy), was administered as a constant infusion (0.28 μmole/kg bw/minute) for 3 hours, starting 1 hour before the beginning of the hyperinsulinemic clamp. Because serum potassium levels tend to fall during this procedure, KCl was given during each study at a

rate of 15 to 20 mEq/hour to maintain the serum potassium between 3.5 and 4.5 mEq/L. The subjects were restudied with the same scheme on a different day when saline was infused instead of L-carnitine. The order of saline and L-carnitine days was randomized. Arterialized blood samples were collected every 30 minutes during the clamp study in order to measure insulin, non-esterified fatty acid (NEFA) and lactate concentrations.

The subjects voided before starting the study; urine was collected during the clamp time to measure the urinary nitrogen loss for each subject, which was used for the calorimetric computations.

Respiratory gas exchange was measured by an open-circuit ventilated hood system (monitor MBM-100, Deltatrac, Datex Instrumentarium Corp. Helsinki). Energy expenditure, respiratory quotient (RQ), and substrate oxidation rate were calculated from the oxygen consumption, the carbon dioxide production, and the nitrogen urinary excretion according to Ferrannini [14]. Respiratory gas exchange measurements were started 60 minutes before starting the study to measure the resting energy expenditure (REE) and continued during the 180 minutes of study.

Analytical Methods

Serum glucose was measured by the glucose oxidase method using a Beckman Glucose Analyzer II (Beckman Instrument, Fullertone, CA, USA). HbA1c was measured by a commercial kit (Bio-Rad, Richmond, CA), normal range 3.5 to 5.5% (CV 5%). Plasma insulin was measured by radioimmunoassay (RADIM, Pomezia, Italy). NEFA were assayed by enzymatic colorimetric method (NEFA Quick, Boehringer Mannheim, Germany). Plasma lactate was measured by an enzymatic method (Boehringer Mannheim, Germany).

Statistical Analysis

All results are expressed as mean±SD. Wilcoxon test was used to evaluate saline vs. L-carnitine infusion data. Mann-Whitney U-test was applied to compare normal control subjects vs. type 2 diabetic patients. A p value of less than 0.05 was considered statistically significant.

For the plasma lactate variable studied repeatedly during the clamp, the period of interest was that between 80 and 120 minutes of the experiment (end-clamp). Values during this period were expressed as variations (increments or decrements) with respect to the relative measured baseline. In order to separate the effect of the treatment from that of the subject, a nested, repeated-measures analysis of variance (ANOVA) was performed for the variables of interest to compare untreated (Carnitine −) and treated (Carnitine +) group.

RESULTS

Table 1 reports the anthropometric characteristics of the studied subjects as well as their baseline values, before the start of the clamping experiment. Basal levels of NEFA were significantly ($p<0.001$) higher in type 2 diabetic patients than in controls; this result might be ascribed to the insulin therapy received by these patients. In fact, it is well known that insulin stimulate free fatty acid synthesis.

During the euglycemic hyperinsulinemic clamp the steady state plasma insulin concentration was 400.8±30.6 and 478.8±72.2 pM in the control and in type 2 diabetic patients respectively (p=n.s.). During the insulin clamp session the steady state plasma glucose concentration was maintained close to the initial values with coefficient of variations ranging from 6.5 to 8%.

Whole body glucose uptake (M-value, Table 2) increased approximately 8% in both groups during L-carnitine infusion compared to saline infusion. In fact, the M value (μmoles/kg_{ffm}/minute) was 48.66±4.73 without carnitine and 52.75±5.19 with carnitine in healthy controls, and 35.90±5.00 vs. 38.90±5.16 in type 2 diabetic patients.

In our series the hepatic glucose production was not measured. However, many studies have shown that endogenous glucose production is completely suppressed under hyperinsulinemic conditions [15,16].

Glucose oxidation, evaluated by indirect calorimetry measurements, significantly increased (Table 2) in type 2 diabetic patients, while in normal controls glucose oxidation under carnitine was not significantly modified from saline infusion value. The difference in total glucose uptake between carnitine and saline infusion was accounted for by a difference in the non

Table 2. Glucose Disposition During the Euglycemic Hyperinsulinemic Clamp

	Control subjects			Type 2 diabetics		
	Saline	Carnitine	p	Saline	Carnitine	p
Whole body glucose uptake rate (M) (μmol/kg/minute)	48.66±4.73	52.75±5.19	<0.001	35.90±5.00	38.90±5.16	<0.001
Glucose oxidation rate (μmol/kg/minute)	25.87±1.64	26.40±3.53	NS	16.25±2.95	17.61±3.33	<0.001
Glucose storage rate (μmol/kg/minute)	22.79±3.46	26.36±3.25	<0.001	19.66±3.04	21.28±3.18	<0.001

The values are normalized for kg of fat-free mass.
Data reported as mean±standard deviation.

oxidative disposal of glucose. Glucose storage was significantly higher in both controls and diabetic patients under carnitine infusion (22.79±3.46 vs. 26.36±3.25 μmoles/kg_{ffm}/minute, $p<0.001$).

Urinary non protein nitrogen loss, averaged 10.8±2.3 and 11.7±2.9 g/24 hour (p=n.s.) in healthy volunteers and type 2 diabetics, respectively.

The two groups of subjects examined showed a significant difference of carnitine-induced alteration of lactate in time, as shown by repeated measurements analysis of plasma lactate levels taking into account group and treatment. The averages of the lactate differences (end clamp-basal) in the groups were as follows: control group, 0.0214±0.0236 without carnitine and 0.00867±0.0502 with carnitine (p=n.s.); diabetic patients, 0.0759±0.0329 without carnitine and 0.0280±0.0191 with carnitine ($p<0.0003$).

DISCUSSION

Our data show that LC infusion during euglycemic hyperinsulinemic clamp improves insulin sensitivity in type 2 diabetic patients. LC determined an about 8% increase over the basal (saline infusion) of whole body glucose uptake in both normal controls and in type 2 diabetic patients. A rise in glucose storage in controls and a balanced increase of both glucose storage and oxidation rates in diabetics accounted for the higher M values found. Ferrannini et al [6] showed that L-carnitine infusion stimulated, by about 17%, whole body glucose utilization in healthy young volunteers. The difference in percent increase between our data and those of Ferrannini et al [6] are likely due to the different experimental procedures. In fact, instead of a priming (3 mmoles)-constant infusion (17 μmoles/minute over 180 minutes) of L-carnitine, we used a constant infusion rate of 0.28 μmole/kg bw/minute for 180 minutes. Therefore, we have probably reached a lower muscular carnitine uptake as a consequence of a delay in the plasma plateau concentration of LC associated with its higher urinary loss.

However, net rates of insulin-induced glucose oxidation were similar with and without carnitine. Consequently, they hypothesized that acute hypercarnitinemia stimulates non-oxidative glucose disposal in the insulinized state, which suggests an increase of the glycogen storage. Our data agree with those of Ferrannini et al [6] for the elevation of the glucose uptake (M) and glucose storage during L-carnitine infusion in healthy volunteers. In addition, we found that the stimulation of whole body glucose disposal effected by L-carnitine was associated with a significant increase in both glucose oxidation and storage in type 2 diabetic patients.

Capaldo et al [7] demonstrated that L-carnitine improves insulin sensitivity in type 2 diabetic patients to the same extent that Ferrannini et al [6] found in control subjects, but they offered no data on substrate oxidation since indirect calorimetry was not performed.

On the basis of our results, L-carnitine infusion stimulates glucose uptake in both healthy subjects and type 2 diabetic patients, whereas the stimulation of glucose oxidation becomes manifest only in diabetic patients.

In type 2 diabetic patients, in whom a defect of the PDH activity is present [17], L-carnitine would normalize PDH activity, thus stimulating oxidative utilization of glucose. In other words, when PDH is normally active, as in the case of the healthy subjects, the excess glucose uptake induced by carnitine could be accumulated in the cells as glycogen. When it overcomes the capability of cell—already highly stimulated by insulin—to oxidize glucose; on the contrary, when PDH activity is impaired, such as in diabetic patients, L-carnitine would enhance it.

Experimental support to this hypothesis derives from the observed fall in plasma concentration of lactate in L-carnitine-infused diabetic patients. An important enzyme catalyzing the rate-limiting step in lactate utilization is PDH, and a decrease in PDH activity would result in a reduction of the oxidation of pyruvate to acetyl-CoA and could contribute to an increased conversion of pyruvate to lactate via lactate dehydrogenase. Mondon et al [18] showed a fourfold increase in lactate production in association with a decrease in the active form of PDH in both fat and skeletal muscle in rats with a form of diabetes that seems to resemble the type 2. Evidence exists that plasma lactate concentrations are increased in type 2 diabetic patients [19] and two- to threefold increase in forearm muscle lactate release has been described in these patients [20,21].

It has been hypothesized that in diabetes mellitus there is a shift in substrate utilization from carbohydrates to lipids [22]: a large proportion of the increase in lipid oxidation is accounted for by an increase in intramuscular triglyceride mobilization. An impaired activity of pyruvate dehydrogenase [5] and an increased activity of β-oxidation enzymes [23] have been described in these patients.

Activation of glycogen synthetase by insulin is decreased in type 2 diabetic patients during euglycemic hyperinsulinemic clamps compared to control subjects [24] and this might contribute to insulin resistance in these patients. The decreased activation of glycogen synthetase by insulin in these patients is related to a decreased activation of glycogen synthetase phosphatase [25]. Insulin-dependent PDH activity also appears to be reduced in type 2 diabetic patients and this reduced enzymatic activity is considered the cause of the reduced insulin-stimulated glucose oxidation observed in these patients [25].

Since there is experimental evidence that L-carnitine stimulates the activity of PDH [1–3], the observation of an increase of oxidative glucose utilization during L-carnitine infusion in diabetic patients could be explained through this mechanism. In our series, we demonstrated a significant fall in the plasma concentrations of lactate after L-carnitine administration. This,

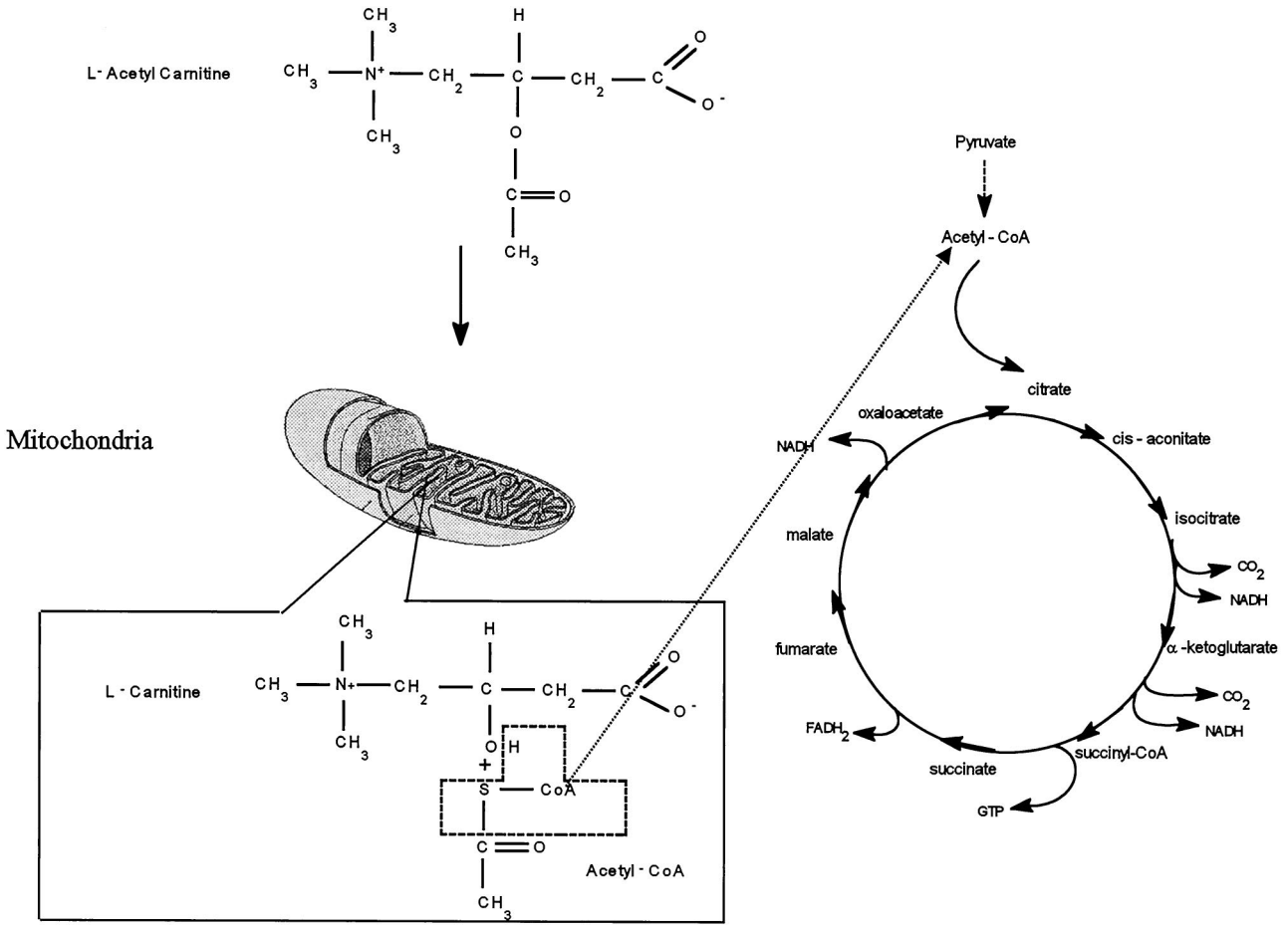

Fig. 1. Mechanism of action of L-acetyl carnitine, which, through the esterification of its alcoholic groups with acetyl-CoA, shuttles acetyl groups across the mitochondria membrane. Then, the acetyl-CoAs enter the Kreb's cycle.

together with the observation of a significantly increased cellular glucose uptake, with higher glucose oxidation in type 2 diabetic patients, suggests an L-carnitine-induced activation of the PDH complex.

In fact, the relative increase of lactate in type 2 patients would reflect a decrease in PDH activity because of a reduction in pyruvate oxidation to acetyl-CoA, which might contribute to an increased conversion of pyruvate to lactate via lactate dehydrogenase. It is not really necessary that PDH be globally reduced, but it is possible that there is a decreased proportion of PDH in its active form in the absence of marked changes in the total amount of the complex, as demonstrated in rats with severe insulin-deficient diabetes [26].

Therefore, in accord with the hypothesis of McGarry on the pathogenesis of insulin resistance [27], it is possible that L-carnitine acts in type 2 diabetic patients by shifting cellular metabolism of fuel substrates toward glucose (Fig. 1). In these patients, who characteristically have an impairment of glucose oxidation and use preferentially fatty acids, carnitine therefore improves the insulin resistance condition typical of the disease.

In conclusion, L-carnitine seems to be a promising drug for the improvement of insulin resistance in type II diabetic patients. Further investigations, however, remain to be conducted in order to ascertain whether an oral formulation might be equally effective.

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