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Original Investigation

Effect of an L-Carnitine–Containing Peritoneal Dialysate on Insulin Sensitivity in Patients Treated With CAPD: A 4-Month, Prospective, Multicenter Randomized Trial

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Background: In peritoneal dialysis, the high glucose load absorbed from dialysis fluid contributes to several metabolic abnormalities, including insulin resistance. We evaluate the efficacy of a peritoneal dialysis solution containing L-carnitine as an additive to improve insulin sensitivity.

Study Design: Multicenter parallel randomized controlled trial.

Setting & Participants: Nondiabetic uremic patients on continuous ambulatory peritoneal dialysis enrolled in 8 peritoneal dialysis centers.

Intervention: Patients were randomly assigned to receive peritoneal dialysis diurnal exchanges with either a standard glucose-based solution (1.5% or 2.5% according to the patient's need) or a glucose-based solution (identical glucose amount) enriched with L-carnitine (0.1%, weight/volume; 2 g/bag) for 4 months, the nocturnal exchange with icodextrin being unmodified.

Outcomes & Measurements: The primary outcome was insulin sensitivity, measured by the magnitude of change from baseline in glucose infusion rate (in milligrams per kilogram of body weight per minute) during a euglycemic hyperinsulinemic clamp. Secondary outcomes were safety and tolerability, body fluid management, peritoneal dialysis efficiency parameters, and biochemistry tests.

Results: 35 patients were randomly assigned, whereas 27 patients (standard solution, n=12; experimental solution, n = 15) were analyzed. Adverse events were not attributable to treatment. Glucose infusion rates in the L-carnitine–treated group increased from 3.8 ± 2.0 (SD) mg/kg/min at baseline to 5.0 ± 2.2 mg/kg/min at day 120 (P = 0.03) compared with 4.8 ± 2.4 mg/kg/min at baseline and 4.7 ± 2.4 mg/kg/min at day 120 observed in the control group (P = 0.8). The difference in glucose infusion rates between groups was 1.3 (95% CI, 0.0-2.6) mg/kg/min. In patients treated with L-carnitine–containing solution, urine volume did not change significantly (P = 0.1) compared to a significant diuresis reduction found in the other group (P = 0.02). For peritoneal function, no differences were observed during the observation period.

Limitations: Small sample size.

Conclusions: The use of L-carnitine in dialysis solutions may represent a new approach to improving insulin sensitivity in nondiabetic peritoneal dialysis patients.

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INDEX WORDS: Carnitine; end-stage renal disease; insulin sensitivity; peritoneal dialysis.

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A key component of peritoneal dialysis (PD) treatment, used by approximately 11% of total dialysis patients,[1] is removal of excess fluid, which is achieved by the addition of an osmotic agent to the solution. Although multiple osmotic agents have been proposed, glucose currently is the standard osmotic agent used due to its efficacy, low cost, delivery of energy source, and acceptable safety profile. However, the detrimental local and systemic effects of the elevated peritoneal glucose load are believed to compromise the longevity of PD patients.[2-4] Absorption of glucose from the dialysate accentuates disturbances of carbohydrate metabolism, which is already impaired in chronic kidney disease. Insulin resistance often is associated with chronic uremia and may cause enhanced morbidity and mortality through an increased occurrence of cardiovascular disease and a protein-energy wasting condition.[5-8]

Thus, strategies devised to reduce/eliminate glucose-associated toxicity and insulin resistance form one of the key objectives of present-day PD research. One option might be to use the naturally occurring substance L-carnitine in the PD solution. We recently have shown that L-carnitine potentially is useful in the PD solution as a safe new osmotic agent.[9] In addition, L-carnitine has been shown to have a favorable effect on glucose metabolism in several reports.[10] The aim of the present proof-of-concept study thus was to evaluate the efficacy of a PD solution containing L-carnitine in patients on continuous ambulatory PD (CAPD). The primary end point was change in insulin sensitivity, evaluated by performing a euglycemic hyperinsulinemic clamp, the gold-standard method for accurate assessment of this metabolic parameter.[11]

METHODS

Study Population

Stable patients with end-stage renal disease (ESRD) 18 years or older on CAPD therapy for at least 3 months were recruited in 8 Italian centers. Each patient gave written informed consent, and approval for the study was given by the local ethics committee for each center.

Prior to entering the study, patients needed to have been treated by CAPD with 2 or 3 diurnal exchanges using standard solutions (1.5% or 2.5% glucose monohydrate, according to the patient's need; Dianeal, Baxter Healthcare) and one nocturnal exchange with icodextrin (Extraneal; Baxter Healthcare) for at least 1 month. Patients were required to have a weekly urea Kt/V $\geq$1.7, weekly creatinine clearance $>$45 L, dialysate to plasma creatinine ratio of 0.50-0.81, and dialysate to plasma glucose ratio of 0.26-0.49 in the peritoneal equilibration test. Patients were excluded if they had received L-carnitine or its derivatives in the previous month or experienced a peritonitis episode in the last 3 months. Other exclusion criteria included type 2 diabetes, hemoglobin level $<$8.5 g/dL, severe diseases or acute infectious conditions, treatment with drugs affecting insulin sensitivity, history of epilepsy or central nervous system disease, pregnancy or lactation, or life expectancy less than 12 months.

For plasma carnitine analyses, blood was drawn from healthy age-matched controls (mean age, 60 $\pm$ 11 [SD] years; n = 8), selected among personnel and relatives of patients at the Chieti PD center.

Study Design

This was a randomized multicenter controlled study with parallel groups to investigate the efficacy of a PD solution containing L-carnitine in patients with ESRD receiving CAPD.

After a 2-week run in, patients were randomly assigned to receive PD diurnal exchanges with either a standard glucose-based solution (control group) or an L-carnitine–enriched solution (intervention group), the nocturnal exchange being unmodified. The treatment period was 120 days. The random allocation of patients was made in blocks composed of 2 intervention and 2 control participants sequentially allocated to each center.

The primary efficacy end point was improved insulin sensitivity as measured by the magnitude of change from baseline in glucose infusion rate (GIR) evaluated by euglycemic hyperinsulinemic clamp. Diabetologists doing the clamp were blinded to the patient's treatment. Secondary outcome measures included safety and tolerability, body fluid management, PD efficiency parameters, and biochemistry tests.

Study Solutions

Study solutions were provided in sterile disposable 2-L bags (Infomed Fluids). Bags had pH of 5.5 and the following composition: sodium, 134 mmol/L; calcium, 1.75 mmol/L; magnesium, 0.5 mmol/L; chloride, 103.5 mmol/L; and lactate, 35 mmol/L. Bags differed in their osmolyte content: glucose monohydrate 1.5% or 2.5% (solutions used by the control group) or glucose monohydrate 1.5% or 2.5% plus 0.1% (weight/volume; 2 g) L-carnitine (solutions used by the intervention group). Glucose concentrations were identical to those used by patients before entering the study.

Study Procedures

After receiving informed consent, a medical history was obtained, physical examination was performed, and blood was drawn (day $-$14). At each subsequent examination (day 0 and then monthly), vital signs and 24-hour urine volume were measured and a medical update (recording all changes in medications, symptom profile, and concomitant diseases) was completed. A 12-lead electrocardiogram evaluating standard parameters was obtained as a safety measure at days 0 and 120. Peritoneal ultrafiltration (calculated as drained $-$ infused volume), parameters of dialysis adequacy (weekly urea Kt/V; creatinine clearance defined as residual renal clearance + dialysate clearance), and peritoneal permeability (by peritoneal equilibration test) also were determined. Blood samples obtained for lipid profile, hematology, and clinical chemistry were analyzed by standard laboratory techniques. Free L-carnitine and acyl-carnitine esters were measured by high-performance liquid chromatography/mass spectrometry.[12] Samples were stored at $-$80°C until measurement at a single laboratory (Analytical Biochemistry and Proteomics Unit, Ce.S.I., Chieti, Italy).

All measurements were performed in a fasting state.

A euglycemic hyperinsulinemic clamp was performed at baseline and study ending, as previously described.[13] Briefly, participants were admitted after a 12-hour overnight fast that included no overnight dialysis exchange to rule out the possibility of residual glucose in the peritoneum. A continuous intrave-

nous insulin infusion was started and maintained at the rate of 40 mU/m^2/min for 120 minutes. Before starting the insulin infusion and at 5-minute intervals thereafter, blood samples were obtained for immediate plasma glucose determination. Infusion of 20% glucose solution was started by means of a separate pump and adjusted to maintain plasma glucose concentration within ±5% of the initial concentration. GIR (in milligrams per kilogram of body weight per minute) was recorded continuously to measure the overall quantity of glucose infused. The average GIR used during the last 30 minutes of insulin infusion to keep plasma glucose level constant was taken as the measurement of insulin sensitivity.

Any adverse events were recorded throughout the treatment period.

Statistical Analyses

Because no previous information from pilot studies was available, power calculation was based on both planned sample size and likely effect (or proof-of-concept effect size). Sample size calculation was based on a previous study[14] in which a euglycemic hyperinsulinemic clamp was used to evaluate the impact of CAPD on patients with ESRD. Hence, using an intermediate standard deviation of 1.7 mg/kg/min of the observed GIR between the pre-CAPD and post-CAPD populations,[14] with 40 patients in each group, we have 80% power (α = 0.05) to detect a difference in the change in estimated GIR between groups of 1.0 mg/kg/min.

Data are reported as mean ± standard deviation. Comparisons were conducted using *t* test for continuous variables and Fisher exact test for categorical variables. Change in GIR (ΔGIR) at 4 months (120 days) was the primary variable tested for the difference between randomized groups. This variable ranged from −3 to 7.5 mg/kg/min and showed deviation from normality (positive skewness) as evaluated by the Shapiro-Wilk test. To reduce positive skewness and improve the normality of the distribution, we applied a data transformation in which we took the logarithm of the sum of ΔGIR and 4. This transformed ΔGIR ranged from 0-2.44 mg/kg/min and showed a negligible deviation from normality. We tested the ΔGIR difference between randomized groups using both untransformed and transformed data.

Statistical significance was evaluated to an α level of 0.05. Statistical analysis was performed using SPSS software, version 11.0 (SPSS Inc).

RESULTS

Although the study had been planned to enroll 40 patients per group, enrollment was terminated after randomization of patient 35 due to difficulty recruiting patients. Of the 35 CAPD patients enrolled, 21

Table 1. Characteristics of Study Population

	Randomly Assigned		Analyzed	
	L-Carnitine Solution	Standard Solution	L-Carnitine Solution	Standard Solution
No. of patients	21	14	15	12
Age (y)	56 ± 13	62 ± 12	56 ± 15	61 ± 13
Sex				
Male	10 (48)	9 (64)	7 (47)	7 (58)
Female	11 (52)	5 (36)	8 (53)	5 (42)
Body mass index (kg/m^2)	26 ± 4	28 ± 5	25 ± 4	28 ± 5
Diastolic BP (mm Hg)	78 ± 9	79 ± 8	78 ± 10	78 ± 9
Systolic BP (mm Hg)	128 ± 12	133 ± 14	130 ± 13	132 ± 15
Heart rate (beats/min)	69 ± 8	71 ± 9	72 ± 7	72 ± 9
Urine output (mL/d)	1,160 ± 570	990 ± 580	1,080 ± 500	1,030 ± 640
Time on dialysis (mo)	24 ± 18	28 ± 30	24 ± 17	29 ± 32
PD daily exchanges				
2 bags	14 (67)	6 (43)	10 (67)	4 (33)
3 bags	7 (33)	8 (57)	5 (33)	8 (67)
PD fluid glucose				
1.5%	20 (95)	13 (93)	15 (100)	12 (100)
2.5%	1 (5)	1 (7)	0 (0)	0 (0)
Weekly urea Kt/V	2.1 ± 0.7	2.0 ± 0.4	2.0 ± 0.5	2.0 ± 0.5
Net drain volume (mL/d)	1,900 ± 2,700	2,400 ± 3,200	1,800 ± 2,800	2,400 ± 3,200
Solute transport (D:P Cr)	0.70 ± 0.05	0.72 ± 0.10	0.70 ± 0.05	0.72 ± 0.10
Creatinine clearance (L/wk)	78 ± 28	80 ± 28	76 ± 27	80 ± 29

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation. No significant difference (Fisher exact test for sex, PD daily exchanges, and PD fluid glucose; *t* test and Mann-Whitney rank sum test for the other characteristics) between the L-carnitine solution and standard solution group for any variable.

Abbreviations and definitions: BP, blood pressure; D:P Cr, dialysate to plasma creatinine ratio during the standard peritoneal equilibration test; net drain volume, difference between total peritoneal drained volume and total peritoneal filling volume; PD, peritoneal dialysis.

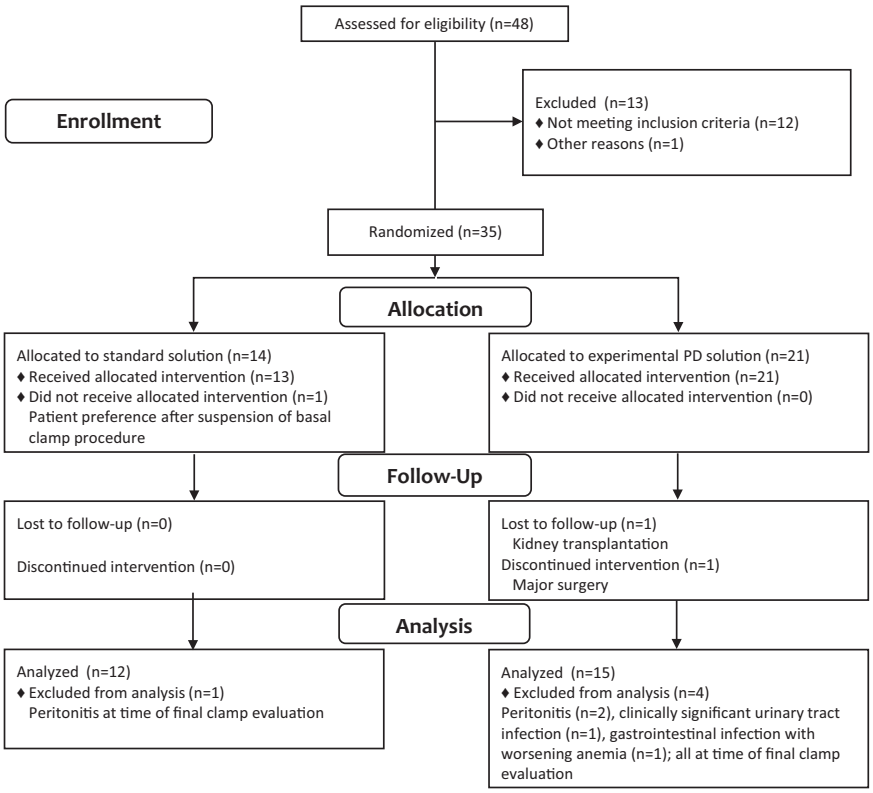

Figure 1. Flow of patients through the study.

were randomly assigned to the intervention group, and 14, to the control group. The number of patients randomly assigned to each group was unequal, but baseline characteristics of the groups did not differ significantly from each other (Table 1).

The patient flow diagram is shown in Fig 1. Fifteen patients in the intervention group and 12 patients in the control group could be analyzed (Table 1). Adverse events were not attributable to treatment.

The majority of patients who completed the study (18 of 27) had GIRs at baseline ranging from 0.5-5 mg/kg/min, which may be considered indicative of severe insulin resistance (Fig 2). In the control group, 4 of 7 insulin-resistant patients showed worsening of insulin sensitivity by the end of the study. In contrast, 9 of 11 insulin-resistant patients in the intervention group had a significant improvement in insulin sensitivity. GIR at baseline did not differ between groups ($P = 0.3$). GIR in the intervention group increased from 3.8 ± 2.0 (SD) mg/kg/min at baseline to 5.0 ± 2.2 mg/kg/min at day 120 ($P = 0.03$) compared with 4.8 ± 2.4 mg/kg/min at baseline and 4.7 ± 2.4 mg/kg/min at day 120 observed in the control group ($P = 0.8$; Table 2). For comparison of the absolute between-group difference in ΔGIR (after logarithmic transformation of each group's ΔGIR), $P = 0.04$. The percentage of change from baseline (relative ΔGIR) was 3% ± 30% and 75% ± 189% in the control and intervention groups, respectively (Table 2); $P = 0.05$ for the between-group comparison of relative ΔGIR. Adjustment for sex[15] did not change results ($P = 0.5$ and $P = 0.5$ for the comparison between absolute or relative ΔGIR values, respectively).

The number of patients treated with 2 or 3 diurnal dialytic solution bags was not statistically significantly different ($P = 0.07$, Fisher exact test; Table 1). In addition, although patients within each study group were exposed to different peritoneal glucose loads, ΔGIR between days 0 and 120 was not significantly different between 2-bag and 3-bag patients in either the intervention (ΔGIR = 0.8 ± 0.8 mg/kg/min for 2 bags and ΔGIR = −0.5 ± 1.1 mg/kg/min for 3 bags; $P = 0.2$ for difference) or control group (ΔGIR = 1.6 ± 2.3 for 2 bags and ΔGIR = 0.5 ± 0.9 for 3 bags; P for difference = 0.3). Moreover, the trial effect in augmenting GIR was roughly independent of the number of bags because the point estimate for the difference between groups was 0.9 (95% confidence interval [CI], −1.7 to 3.4) in 2-bag and 0.9 (95% CI, −0.4 to 2.3) in 3-bag patients. However, because of the reduction in sample size, differences were not statistically significant in either the 2-bag ($P = 0.5$) or 3-bag ($P = 0.2$) groups.

Compared with age-matched healthy controls (48 ± 7 years of age; n = 8), plasma levels of

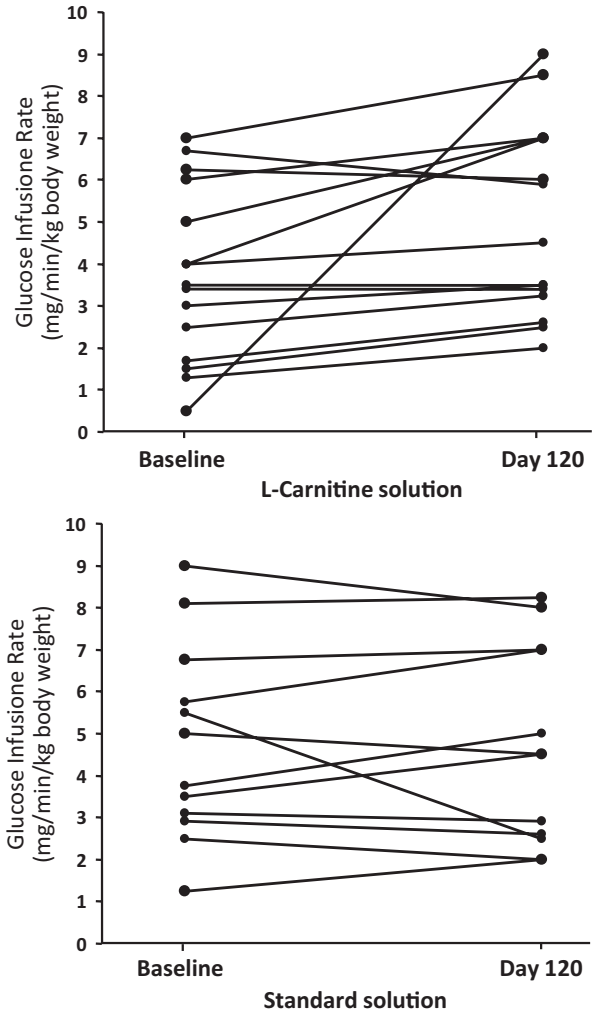

Figure 2. Insulin sensitivity as assessed by measurement of the glucose infusion rate during euglycemic hyperinsulinemic clamp in continuous ambulatory peritoneal dialysis patients treated for 120 days with L-carnitine–containing (n = 15; upper) or standard (n = 12; lower) solutions for diurnal exchanges.

L-carnitine (in micromoles per liter) at baseline were significantly lower ($P = 0.04$) in both the control (36 ± 13 μmol/L) and intervention (38 ± 9 μmol/L) groups. Plasma levels of L-carnitine and its major metabolic congener, acetyl-carnitine, increased in patients treated with the experimental solution, reaching an apparent steady state after 30 and 60 days, respectively (Table 3). Recovery of L-carnitine from the drained dialysate showed that significant amounts of L-carnitine along with acetyl-carnitine are excreted by the peritoneal route and, as seen in plasma, a similar apparent steady state was achieved for both compounds (Table 3). In the control group, no change in carnitine levels was observed in plasma or drained dialysate throughout the study period (data not shown).

Tolerance to the experimental PD solution was good, and no patient reported discomfort/pain during infusion. Body weight, blood pressure, and heart rate did not differ significantly either between or within groups, and physical examination and electrocardiographic findings were unmodified (data not shown).

With regard to parameters of dialysis efficiency (Table 4), weekly urea Kt/V showed a slight but significant decrease in both groups, whereas creatinine clearance and peritoneal ultrafiltration volume did not change. Peritoneal permeability for glucose and creatinine showed no significant variations (Table 4). In terms of daily urine output, a significant decrease (from 970 ± 670 to 690 ± 500 mL/d; $P = 0.02$) was observed in the control group, whereas urine output did not change in the intervention group (from 1,070 ± 500 to 960 ± 420 mL/d; $P = 0.1$; Fig 3).

Table 4 also lists metabolic characteristics of the study groups. Fasting plasma glucose levels were not statistically different. Within the control group, but not the intervention group, a significant increase was found in plasma insulin levels ($P = 0.04$; Table 4). A moderate but significant increase in plasma triglyceride ($P = 0.004$) and total cholesterol levels ($P = 0.05$) was observed in the intervention group. Changes in triglyceride ($P = 0.04$) and low-density lipoprotein cholesterol levels ($P = 0.04$) were statistically different when comparing the 2 groups, whereas total cholesterol, high-density lipoprotein (HDL) cholesterol, and non-HDL cholesterol levels were not (Table 4). A statistically significant decrease in HDL cholesterol level ($P = 0.03$) was found in the control group (Table 4).

Other laboratory parameters included hemoglobin, white blood cell count, platelet count, serum sodium, potassium, calcium, phosphorus, total protein, albumin, aspartate and alanine aminotransferase, alkaline phosphatase, γ-glutamyl transferase, total bilirubin, fibrinogen, C-reactive protein, blood urea nitrogen, and creatinine. No significant difference between or within study groups was observed (data not shown).

DISCUSSION

Insulin resistance is common in patients with ESRD and constitutes a key therapeutic target for reduction of excess cardiovascular mortality in these patients.[7,11] Although this situation is corrected in part after initiation of dialytic therapy, excessive intraperitoneal glucose absorption during PD has many potential systemic metabolic effects, including insulin resistance due to carbohydrate load, caloric uptake, and hyperglycemia.[3,7]

Table 2. GIR During Euglycemic Hyperinsulinemic Clamp

Within-Group Difference

		GIR (mg/kg/min)				
	No.	Day 0	Day 120	ΔGIR	95% CI	*P*
Control	12	4.8 ± 2.4	4.7 ± 2.4	−0.1 ± 1.2	−0.8 to 0.7	0.8
Intervention	15	3.8 ± 2.0	5.0 ± 2.2	1.2 ± 2.0	0.1 to 2.3	0.03

Between-Group Difference

	Difference in ΔGIR	95% CI	*P*
Absolute	1.3 ± 1.7[a]	0.0 to 2.6	0.06, 0.04[b]
Percentage	72% ± 143%[c]	−42% to 185%	0.2, 0.05[b]

Note: In patients receiving continuous ambulatory peritoneal dialysis treated for 120 days with L-carnitine–containing (intervention) or standard solutions (control) for diurnal exchanges. Unless otherwise indicated, values are given as mean ± standard deviation.

Abbreviations and definitions: CI, confidence interval; ΔGIR, change in GIR from baseline to day 120; GIR, glucose infusion rate.

[a]Between-group difference in mean ΔGIRs.

[b]First *P* value based on untransformed data; second *P* value based on log-transformed data.

[c]Between-group difference in mean values of 100×(ΔGIR)/baseline GIR.

The present trial is to our knowledge the first to show the insulin-sensitizing effect of a PD solution containing L-carnitine in nondiabetic patients with ESRD on CAPD therapy. The presence of L-carnitine in the solution led to a statistically significant increase in insulin sensitivity. Moreover, a statistically significant increase in fasting plasma insulin levels between days 0 and 120 was observed within the control but not the intervention group. Altogether, these findings are in line with several studies conducted in healthy, insulin-resistant, and diabetic persons with normal kidney function,[10,16,17] as well as in patients with ESRD on hemodialysis therapy,[18,19] showing improved glucose homeostasis and insulin sensitivity after L-carnitine or prodrug administration.

A potential key element regarding the beneficial action of L-carnitine on insulin resistance is the possibility to increase L-carnitine exposure in insulin target organs.[10,17] The location of insulin resistance in uremia is confined to skeletal muscle.[20] In skeletal muscle of people with diabetes and/or who are insulin resistant, insulin seems incapable of mediating the switch from lipid to carbohydrate oxidation, a state described as "metabolic inflexibility."[10,21] The impaired muscle glucose disposal observed in these individuals may be associated with pyruvate dehydrogenase kinase activation by an increased pool size of intramitochondrial acetyl coenzyme A (acetyl-CoA), thereby keeping pyruvate dehydrogenase in a less active state.[22] An increase in availability of L-carnitine in the cell may reduce the intramitochondrial acetyl-CoA pool and hence relieve acetyl-CoA activation of muscle and liver pyruvate dehydrogenase kinase by shifting the freely reversible L-carnitine acetyltransferase-catalyzed reaction toward acetyl–L-carnitine formation. This is reflected in our and other studies by a significant increase in plasma acetyl-carnitine in L-carnitine–treated patients and a significant increase in whole-body glucose disposal.[23]

Dialysis therapy is known to lead to a state of L-carnitine deficiency,[10] as also observed at baseline in our patients. In the intervention group, plasma L-carnitine and acetyl-carnitine levels markedly increased, achieving an apparently steady state after 30-60 days. This was associated with an enhancement in L-carnitine loss in PD fluid drained from the peritoneal cavity, which again reached an apparently steady state after 30 days. These findings may suggest that apparent equilibrium between L-carnitine absorption, exposure, and excretion was achieved.

L-Carnitine urinary loss also may have contributed to the apparent reaching of a safe steady state for plasma concentrations of L-carnitine and acetyl-carnitine. Carnitinuria might be expected considering that the tubular active transport system of filtered carnitine is saturated at an L-carnitine concentration of about 60-100 μmol/L[10] and that plasma L-carnitine exposure achieved in L-carnitine–treated patients was >1 mmol/L. Increased L-carnitine urinary excretion also could explain at least in part the better preservation of urine volume in CAPD patients treated with L-carnitine–containing solution compared with controls, which may signify an osmotically driven maintenance of diuresis having L-carnitine osmotic properties.[9,24,25] This observation may have clinical relevance because urine output in PD patients is important in maintaining

Table 3. Plasma and Dialysate Concentrations of Free Carnitine and Acetyl-Carnitine

	Plasma Free Carnitine (μmol/L)			Plasma Acetyl-Carnitine (μmol/L)			Dialysate Free Carnitine (μmol/L)			Dialysate Acetyl-Carnitine (μmol/L)		
Time (d)	All Patients	2 Bags	3 Bags	All Patients	2 Bags	3 Bags	All Patients	2 Bags	3 Bags	All Patients	2 Bags	3 Bags
0	38 ± 9[a]	41 ± 9[a]	30 ± 7[a]	6.6 ± 1.1[a]	7 ± 5[a]	6 ± 2[a]	30 ± 8[a]	32 ± 7[a]	26 ± 9[a]	7 ± 3[a]	7 ± 4[a]	7 ± 3[a]
30	1,160 ± 391	987 ± 218	1,578 ± 287	292 ± 182	233 ± 137	450 ± 157	1,146 ± 551	1,634 ± 623	903 ± 320	320 ± 173	248 ± 128	464 ± 171
60	1,041 ± 312	932 ± 195	1,364 ± 272	296 ± 194	253 ± 176	430 ± 196	979 ± 395	1,414 ± 335	805 ± 265	397 ± 228	296 ± 162	651 ± 165
90	1,293 ± 550	1,093 ± 219	1,850 ± 672	399 ± 276	342 ± 227	550 ± 374	1,140 ± 334	1,474 ± 302	991 ± 230	474 ± 227	378 ± 181	690 ± 171
120	1,122 ± 438	902 ± 189	1,701 ± 331	396 ± 263	313 ± 203	613 ± 322	1,142 ± 421	1,594 ± 233	941 ± 314	441 ± 251	318 ± 183	720 ± 116

Note: In patients receiving continuous ambulatory peritoneal dialysis who were treated with L-carnitine–containing solution bags for diurnal exchanges during study period. Values are given as mean ± standard deviation.

[a] $P < 0.001$ in comparison to 30, 60, 90, and 120 days.

fluid balance, and its loss cannot be replaced by simply increasing the dose of PD.[26]

At the end of the study, we observed stability in the parameters of peritoneal membrane transport and dialysis adequacy, with the exception of a decrease in weekly urea Kt/V in both PD groups. Although most laboratory parameters also proved to be stable, a moderate although statistically significant increase in plasma triglyceride level was found in the intervention group. A slight increase in total cholesterol level was seen within the intervention group, along with a slight decrease in HDL cholesterol level within the control group. We did not observe other changes in lipid levels. Furthermore, at the end of the study, levels of cardiovascular biomarkers such as fibrinogen and C-reactive protein were not statistically different from baseline in either group, suggesting that L-carnitine does not alter inflammatory status.

It is worth noting that Chowienczyk et al[27] and Jonkers et al[28] have independently shown that insulin resistance rather than hypertriglyceridemia per se is associated with endothelial dysfunction in chronic hypertriglyceridemia. Endothelial function is impaired in PD patients, and along with overhydration, protein-energy wasting, insulin resistance, and calcification, it is believed to be an important cardiovascular risk factor in this patient population.[6] Less convincing evidence is available to suggest that dyslipidemia and/or a high atherogenic lipid profile in dialysis patients is associated directly with cardiovascular risk,[6,29,30] even when treated with statins and/or ezetimibe,[31-33] or with the association of niacin to simvastatin.[34]

Due to the many laboratory parameters that we tested, the significant increase in plasma triglyceride level may have occurred by chance. However, if the increase is real and causally linked to L-carnitine treatment, it may be speculated that this might reflect simply improved hepatic insulin sensitivity, particularly in patients exposed to a large and constant glucose load.[35-37] Moreover, due to the differential hepatic insulin resistance of Forkhead box protein O1 (FoxO1) versus sterol regulatory element-binding protein 1c (SREBP-1c),[38,39] improving insulin sensitivity in patients exposed to a high carbohydrate load would not only stimulate lipogenesis, but also promote very low-density lipoprotein–triglyceride secretion in the liver.[40,41] Last but not least, carriers of polymorphisms in the glucokinase regulatory protein gene have lower fasting glycemia and insulin resistance and are defended against the development of diabetes even with hypertriglyceridemia.[42,43]

Table 4. Changes From Baseline and Between-Group Differences for a Variety of Criteria According to Treatment Group

	Standard Solution (n = 12)			L-Carnitine Solution (n = 15)			
	Day 0	Day 120	Percentage Change[b]	Day 0	Day 120	Percentage Change[b]	*P*[a]
Dialysis efficiency parameters							
Urea Kt/V (weekly)	2.0 ± 0.5	1.6 ± 0.5	−15 ± 27[c]	2.0 ± 0.5	1.7 ± 0.5	−10 ± 21[c]	0.4
Net drain volume (mL/d)	710 ± 700	1,050 ± 390	18 ± 150	730 ± 480	800 ± 350	−3 ± 33	0.6
D:P creatinine	0.72 ± 0.11	0.71 ± 0.14	−1 ± 13	0.70 ± 0.05	0.69 ± 0.09	−2 ± 14	0.8
D:P glucose	0.39 ± 0.18	0.40 ± 0.13	17 ± 46	0.35 ± 0.06	0.31 ± 0.07	−9 ± 23	0.3
Creatinine clearance (L/wk)	80 ± 31	74 ± 21	−4 ± 15	78 ± 27	76 ± 32	2 ± 36	0.7
Metabolic characteristics							
Glucose (mg/dL)	92 ± 16	92 ± 19	2 ± 27	92 ± 17	86 ± 11	−5 ± 16	0.4
Insulin (μU/mL)	13 ± 9	21 ± 19	55 ± 57[c]	12 ± 9	13 ± 10	20 ± 38	0.07
Triglycerides (mg/dL)	197 ± 114	223 ± 143	14 ± 32	181 ± 81	301 ± 153	83 ± 96[d]	0.04
Total cholesterol (mg/dL)	193 ± 84	186 ± 41	3 ± 21	191 ± 36	217 ± 61	13 ± 20[c]	0.1
HDL cholesterol (mg/dL)	48 ± 15	41 ± 10	−13 ± 13[c]	42 ± 12	39 ± 12	−5 ± 23	0.3
LDL cholesterol (mg/dL)	132 ± 57	106 ± 35	−15 ± 18	106 ± 35	112 ± 48	3 ± 20	0.04
Non-HDL cholesterol (mg/dL)	177 ± 84	161 ± 38	1 ± 28	148 ± 36	181 ± 67	21 ± 33	0.1

Note: Unless otherwise indicated, values are given as mean ± standard deviation. Conversion factors for units: glucose in mg/dL to mmol/L, ×0.05551; triglycerides in mg/dL to mmol/L, ×0.01129; total, HDL, LDL, and non-HDL cholesterol in mg/dL to mmol/L, ×0.02586.

Abbreviations and definitions: D:P, dialysate to plasma ratio during the standard peritoneal equilibration test; HDL, high-density lipoprotein; LDL, low-density lipoprotein; net drain volume, difference between total peritoneal drained volume and total peritoneal filling volume.

[a] *P* for the comparison between delta (effect of the L-carnitine solution).

[b] Percent of mean value's change from baseline.

[c] $P < 0.05$ for the comparison of day 120 versus day 0.

[d] $P < 0.01$ for the comparison of day 120 versus day 0.

Our study has some obvious limitations. The number of patients studied is relatively small. The main reasons for that were difficulty recruiting patients according to the study's criteria of eligibility (ie, not many CAPD patients available on icodextrin plus at least 2 diurnal exchanges with glucose) and patient readiness to undergo the clamp study. These constraints forced us to use inadequate sample sizes (from a statistical standpoint) for practical reasons. It is well recognized that low power increases the probability of type II error. But this was not our case because we found a positive effect. However, we recognize that low statistical power may affect the interpretation of our findings, although it also should be considered that the observed ΔGIR difference between groups was higher (1.3 mg/kg/min) than that originally estimated according to our sample size calculation. We noted a lower baseline GIR in the intervention (L-carnitine) group. Thus, the regression to the mean may have contributed at least in part to the difference between groups. However, participants were randomly allocated to groups and thus the responses from all groups should be affected equally by regression to the mean. It also should be taken into account that a higher baseline GIR may even indicate that the control group was more insulin sensitive. This would not favor the effect of the treatment on insulin sensitivity; despite this, we saw an increase in insulin sensitivity in the intervention group. Patients treated with 3 bags were exposed to a higher glucose load than those treated with 2 bags, and this might have affected insulin sensitivity because in the intervention group, there were more patients treated with 2 bags. However, although several studies have addressed this issue by replacing long-dwell exchanges with icodextrin to significantly lower glucose absorption, not all have shown that icodextrin improved glycemic status in diabetic[44,45] and nondiabetic[46] PD patients. Finally, appropriate concentrations of the components of the dialysate mix still need to be defined, particularly in low and high peritoneal transporters, because such patients were excluded from the present study.

Notwithstanding this, use of L-carnitine in the PD solution may be a fruitful new approach for combating glucose-associated toxicity. We previously have shown that L-carnitine works as an osmotic agent with efficiency comparable to that of glucose.[9] L-Carnitine may be even more effective, offsetting some of the local toxic effects of glucose.[9,47] In addition, the present study shows that L-carnitine in PD fluid can have systemic metabolic benefits. Possessing both

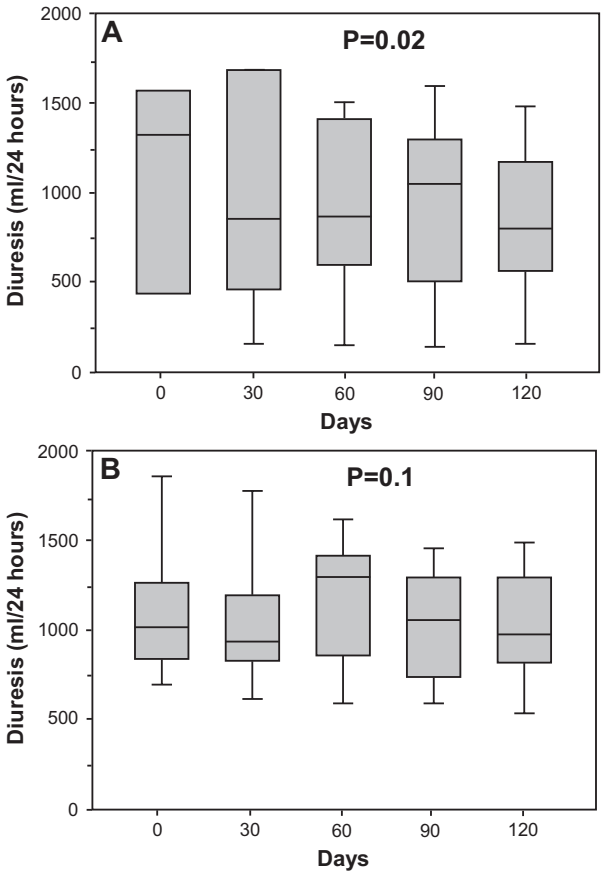

Figure 3. Daily urine volume in continuous ambulatory peritoneal dialysis patients treated with (A) standard (n = 12) or (B) L-carnitine–containing solutions (n = 15).

osmotic properties and favorable metabolic action, L-carnitine may be proposed as the prototypical osmometabolic agent for use in PD.

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