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# 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-

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