Carnitine has an essential role in the mitochondrial oxidation of long-chain fatty acids. Carnitine deficiency has been described in patients with chronic kidney disease.

Total carnitine (TC) deficiency or a lower-than-normal ratio of free carnitine to acylated carnitine (FC:AC) has been shown to be associated with disorders in metabolism and plasma lipids. Metabolism and therapeutic use of carnitine have therefore been a major area of interest in dialysis patients.

In a prospective observational study, we determined carnitine status (TC and FC:AC) and its correlations with lipid plasma levels in peritoneal dialysis (PD) and hemodialysis (HD) patients. In pediatric patients on chronic PD or HD, we evaluated nutritional status (weight and height), biochemical parameters (TC, FC, and AC levels), and fasting plasma lipoprotein concentrations.

We studied 35 patients (16 boys, 19 girls; 25 on PD, 10 on HD). Median age was 5 years (range: 3 months – 15 years). Median weight-to-height Z-score was −0.5 (range: −2.1 to 1.9), and median height-to-age Z-score was −2.5 (range: −0.3 to −2.9). The mean TC was 65.4 ± 23.8 pg/mL (normal value: 40 – 55 pg/mL); the median AC was 18 pg/mL (range: 2 – 56 pg/mL; normal value: 3 – 15 pg/mL); and the mean FC was 41.8 ± 16.6 pg/mL (normal value: 25 – 35 pg/mL). Median serum FC:AC was 2.22 (range: 0.59 – 4.3; normal value: 4). A significantly higher AC and a lower FC:AC were observed in HD patients as compared with PD patients. No differences in TC and FC were observed when patients were grouped by dialysis modality, time on dialysis, or nutrition status. Total cholesterol was 200 mg/dL or higher in 20 patients, and 25 patients showed elevated triglycerides (>150 mg/dL). The latter patients had a higher AC than did the group of patients with triglycerides below 150 mg/dL (AC: 22 pg/mL and 12.5 pg/mL respectively; Kruskal–Wallis p < 0.003).

We found TC levels to be high in this group of patients. However, the FC:AC ratio was lower than normal in all except in 1 patient. Elevated triglycerides were associated with elevated AC, suggesting carnitine insufficiency in our patients.

Key words
Carnitine, fatty-acid metabolism, end-stage renal disease, free carnitine, acylated carnitine, free carnitine: acylated carnitine ratio

Introduction
Abnormalities of lipid metabolism develop frequently in patients on chronic dialysis (1). The pathogenesis of these abnormalities is multifactorial, and it has been postulated that reduced levels of carnitine may interfere with fatty-acid metabolism (2).

Carnitine is a low-molecular-weight compound obtained from the diet that is also biosynthesized mainly in the liver, kidney, and brain from the essential amino acids lysine and methionine (3). The primary role of L-carnitine is transfer of long-chain fatty acids across the inner mitochondrial membrane for subsequent oxidation. Thus, L-carnitine plays a critical role in lipid catabolism (4–7). Because of this role in
fatty-acid oxidation, endogenous concentrations of L-carnitine and its acyl derivatives are maintained within relatively narrow limits (8).

In mammals, carnitine is present as free carnitine (FC) and acylated carnitine (AC). The latter is a product of reactions that involve the transfer of acyl groups from acyl coenzyme A. Typically, in healthy humans, approximately 80% – 85% of carnitine exists as the free form in plasma (9).

Physiologic abnormalities caused by inadequate carnitine metabolism may be associated with either decreased absolute content of FC or a lower-than-normal FC:AC ratio (the normal ratio is 4:1). These conditions have been respectively described as carnitine deficiency and carnitine insufficiency. The two conditions may coexist—for example, in patients with kidney failure undergoing dialysis (5).

It was suggested by Bohmer et al. that chronic hemodialysis (HD) therapy causes carnitine deficiency (2). Such a disturbance was later confirmed by other investigators (10–12). However, in the literature, findings on carnitine status in adult patients receiving peritoneal dialysis (PD) are conflicting. Normal (13–16), low (17), and high (18) plasma levels of total carnitine (TC) have been reported. Also, studies analyzing plasma levels of FC and esterified carnitine fractions in continuous ambulatory PD (CAPD) patients have noted either normal (19,20) or low (19,21–24) FC levels and a low FC:AC. Only three studies involving 34 patients have been published describing the carnitine status of pediatric PD patients (21,25,26). Two of those studies (25,26) showed TC levels similar to those in healthy controls, and the third (21) reported low carnitine levels in patients receiving CAPD treatment for longer than 4 months.

In children on PD, the results for measured carnitine levels are contradictory, but the usual observation is that plasma TC is not different from that measured in controls, but plasma FC is significantly lower and AC is higher (20,27,28). Higher daily losses of free carnitine in PD fluid may contribute to these disturbances (24).

Carnitine metabolism and therapeutic use of carnitine has been a major area of interest in dialysis patients. In the present study, we determined carnitine status (TC and FC:AC) and its correlations with lipid plasma levels in peritoneal dialysis (PD) and hemodialysis (HD) patients.

**Patients and methods**

We included 25 PD and 10 HD pediatric patients who did not suffer from any systemic diseases in the study. None had received carnitine supplementation. Patients were ambulatory and were being treated at the nephrology and nutrition units of the Luis Calvo Mackenna Children’s Hospital in Santiago, Chile. The underlying causes of end-stage renal diseases were renal dysplasia ($n = 20$), reflux nephropathy ($n = 2$), hemolytic uremic syndrome ($n = 4$), obstructive uropathy ($n = 2$), chronic glomerulonephritis ($n = 6$), and unknown ($n = 1$). No patient had suffered from nephrotic syndrome during the preceding 6 months or used medications influencing lipid metabolism (lipid-lowering drugs, beta-blockers, glucocorticoids). The protocol was evaluated and approved by the Ethics Committee of the Hospitals, and written informed consent was obtained from the children’s parents before the study was initiated.

**Anthropometry**

Weight of the child in minimum clothing was measured on a mechanical Seca scale (Seca, Hamburg, Germany) with 0.1-kg precision and 150-kg capacity. Children on PD were weighed with a known dialysate volume in the peritoneal cavity, and the observed weight was adjusted accordingly. Children on HD were weighed after a dialysis session. Recumbent length was measured in subjects younger than 2 years, and in older children, standing height was measured (to 1-mm precision in both cases). Nutrition status was classified according to the National Center for Health Statistics standards, based on Z-score index (29).

**Biochemical measurements**

A fasting lipid profile and levels of TC, FC, AC [by a radio-enzymatic method (30)] were obtained after a 12-hour overnight fast. Blood samples were drawn into tubes containing ethylenediaminetetraacetic acid. Concentrations of serum total cholesterol, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were determined enzymatically (Boehringer Mannheim, Mannheim, Germany). Low-density lipoprotein cholesterol (LDL-C) levels were calculated as the difference between total cholesterol and HDL-C (Friedewald formula).

The National Cholesterol Education Program and the National Kidney Foundation’s 2005 Kidney Disease Outcomes Quality Initiative were used to categorize dyslipidemia.
Statistical analysis
Means, standard deviations, correlation coefficients, and t-tests were performed using Microsoft Excel, version 5.0 (Microsoft Corporation, Redmond, WA, U.S.A.), and Statistica for Windows, version 4.5 (StatSoft, Tulsa, OK, U.S.A.). A value of \( p < 0.05 \) was accepted as statistically significant. The Fisher exact test was used to assess associations between laboratory values and other variables.

Results
Our study included 35 patients (16 boys, 19 girls; 25 on PD, 10 on thrice-weekly HD). Median age was 5 years (range: 3 months – 15 years). Median weight-to-height Z-score was –0.5 (range: –2.1 to 1.9), and median height-to-age Z-score was –2.5 (range: –0.3 to –2.9). Both groups were similar for all characteristics, with exception of median age (Table I).

The full group had a high mean levels of TC (65.4 ± 23.8 pg/mL) and FC (41.8 ± 16.6 pg/mL), and a high median AC (18 pg/mL; range: 2 – 56 pg/mL), as compared with the respective normal values (40 – 55 pg/mL, 25 – 35 pg/mL, and 3 – 15 pg/mL). The median FC:AC was lower than normal [2.22; range: 0.59 – 4.3; normal value: 4 (6)].

A significantly higher AC and a lower FC:AC were observed in patients on HD than in those on PD. No statistically significant differences were observed in TC and FC when the patients were grouped by dialysis modality, time on dialysis, or nutrition status (Table II).

Both groups showed high TG (>150 mg/dL) and total cholesterol (≥200 mg/dL), without any differences between the dialysis modalities by chi-square analysis.

Discussion and conclusions
Disturbances in carnitine pool homeostasis during dialysis have been implicated as a contributing factor in abnormalities of fatty-acid metabolism (2). Dialytic losses of carnitine, combined with reduced renal synthesis and lowered intake of meat and dairy products (dietary source of carnitine), have been suggested as a cause of carnitine deficiency in the end-stage renal disease population (31–33).

Studies in pediatric patients receiving dialysis have shown conflicting results on carnitine status (20,25–27), and most studies in HD populations have found carnitine deficiency (2,34). In the present study, the first observational study designed to evaluate carnitine status in children on both PD and HD, total carnitine concentrations were unexpectedly high in both groups. These findings contrast with observations by Murakami et al. (21), who reported decreased TC levels in children receiving CAPD for more than 4 months.

Of all the patients, 71% were hypertriglyceridemic, and 57% were hypercholesterolemic, with 90% showing one of these two conditions. When we compared HD patients with PD patients, we found that children on PD showed higher total cholesterol, LDL-C, and total cholesterol:LDL-C, as shown in Table III.

Patients with TG > 150 mg/dL showed a higher AC than did those with TG < 150 mg/dL (22 pg/mL and 12.5 pg/mL respectively, Kruskal–Wallis \( p < 0.003 \); Table IV).

<table>
<thead>
<tr>
<th>Table I</th>
<th>Demographic and dialysis data for the study patients</th>
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<tbody>
<tr>
<td></td>
<td>PD (n = 25)</td>
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<tr>
<td>Age (years)</td>
<td>4.4 (range: 3 mo. – 15 yr.)</td>
</tr>
<tr>
<td>Sex (boys/girls)</td>
<td>13/12</td>
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<tr>
<td>Time on dialysis (months)</td>
<td>7</td>
</tr>
<tr>
<td>Weight-to-height Z-score</td>
<td>–0.26±1</td>
</tr>
</tbody>
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\(^a\) Kruskal–Wallis test.
\(^b\) Fisher exact test.
\(^c\) Student \( t \)-test.

PD = peritoneal dialysis; HD = hemodialysis; NS = nonsignificant.
On the other hand, we found a significantly higher AC level and a lower FC:AC index in the full group—and especially in HD patients as compared with PD patients. This result probably reflects the fact that FC is a water-soluble substance with a molecular weight of 162 Da, which could be easily be lost during dialysis. Plasma AC has a greater molecular weight and may be maintained unchanged because of the molecular weight difference (35).

Because FC and AC exist in a dynamic balance, a normal FC:AC ratio is required to maintain normal oxidative processes in mitochondria, and lipid metabolism shows an association with change in that ratio (36). Low FC and FC:AC ratio have both been described as carnitine insufficiency (5), which has been proposed by others as evidence of impaired mitochondrial beta-oxidation, with concomitant increase in medium- and long-chain acylcarnitines in serum (37,38) in dialysis patients.

The difference in the median age of the two modality groups should not be important, given that previous investigations have demonstrated no significant effect of age on serum carnitine concentrations (39). In addition, the present study confirms the high prevalence of hypertriglyceridemia and hypercholesterolemia in these patients (1,27,40). The high percentage of patient with hypertriglyceridemia and hypercholesterolemia could be related to carnitine insufficiency, but the causes and significance of these findings remain to be evaluated.

Because information on carnitine deficiency in children with end-stage renal disease and dialysis is scarce (41), we hope that this article will serve to stimulate further research in children.

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References


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Corresponding author:
Veronica B. Marín, MD, University of Chile, Hernando de Aguirre 1778, Apartment 204, Providencia, Santiago, Chile.

E-mail:
veronica.marinbriano@gmail.com