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Free and esterified carnitine in continuous ambulatory peritoneal dialysis patients

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Free and esterified carnitine in continuous ambulatory peritoneal dialysis patients. Free, acetyl-, medium- and long-chain acylcarnitine and total plasma carnitine concentrations were measured in eight continuous ambulatory peritoneal dialysis (CAPD) patients and eight age- and sex-matched healthy controls. Daily loss of carnitine was also quantified in both groups, by analysis of urine and dialysis fluid. Plasma total carnitine concentration in CAPD patients was not significantly different from controls (42.8 ± 1.6 and 43.1 ± 2.3 μmol/liter, respectively). However, the plasma free carnitine concentration of CAPD patients was significantly lower than that of controls (28.5 ± 1.4 and 36.2 ± 2.5 μmol/liter, respectively; $P < 0.05$). No difference in the daily loss of total carnitine was found between CAPD patients and controls (269.7 ± 30.0 and 240.5 ± 33.0 μmol, respectively), but the daily loss of free carnitine was significantly greater in CAPD patients (175.8 ± 17.3 and 105.8 ± 16.4 μmol, respectively; $P < 0.05$). The ratio of total acylcarnitine (acetyl-, medium- and long-chain acylcarnitine) to free carnitine was significantly greater in plasma of CAPD patients than in controls ($P < 0.01$) and was lower in daily fluid losses ($P < 0.001$). These ratio differences suggests that an alteration in acyl group metabolism is occurring in CAPD patients. This may be attributable to an accumulation of medium- and long-chain acylcarnitine in liver of CAPD patients which would be exchanged for plasma free carnitine and/or to a differential loss of free and acylcarnitine across the peritoneal cavity.

Carnitine is a naturally occurring compound which is involved not only in muscular energy metabolism but also in overall cellular metabolism. It is an essential factor in long-chain fatty acid oxidation, facilitating the translocation of fatty acyl groups across the inner mitochondrial membrane [1]. Carnitine may also regulate the cytosolic/mitochondrial acyl-CoA/CoASH ratio, by buffering excess acyl group formation as a result of an impairment in the cellular metabolism [2] or an increase in the rate of cellular energy metabolism [3], and by doing so may prevent the inhibition of many cellular reactions which depend on existence of a viable pool of CoASH. Carnitine has become of interest in renal failure because it has been shown that patients with end-stage renal failure on hemodialysis have subnormal plasma and muscle free carnitine and/or elevated acylcarnitine concentrations [4–8], although the decline in muscle carnitine concentration has not been consistently confirmed [9, 10]. It is possible that these deficiencies attributed to the loss of carnitine during hemodialysis could contribute to the muscular fatiguability and weakness that renal failure patients experience. Whether a similar situation exists in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) is unclear. Previous studies have shown plasma carnitine of CAPD patients to be comparable [6, 7, 11–13], towards being lower [8] or significantly lower [14] compared with controls. However, the controls in these previous studies were not age- and sex-matched, which would have been desirable since plasma carnitine is influenced by these two factors [15, 16], and may therefore explain these equivocal findings.

The aims of the present study therefore were to assess the plasma carnitine status of CAPD patients and to quantify the daily loss of carnitine in this patient group compared with age- and sex-matched healthy control subjects.

Methods

Eight patients (mean age 43.6 ± 4.8 years; range 20 to 60 years; Table 1) undergoing CAPD treatment (mean duration 27 months ± 14; range 4 to 120 months) were recruited from those attending the CAPD out-patient clinic and matched with age- and sex-healthy controls. The mean age of controls was 43.3 ± 4.7 years (range 20 to 59 years; Table 1). A 10 ml sample of venous blood was obtained at least seven hours post-prandially from an antecubital vein and was mixed with lithium heparin. Following centrifugation (10 min at 3,000 rpm), the plasma was snap frozen in liquid nitrogen and stored at −80°C.

Both controls and CAPD patients undertook a 24-hour urine collection using a 2 liter container containing 5 ml of a 0.67 mol/liter thymol solution in isopropanol. CAPD patients also collected their dialysate fluids over the same period as their 24-hour urine sample. Following collection, the contents of each dialysis bag and urine collection were pooled, mixed thoroughly and 2 aliquots (10 ml) of each fluid were removed, snap frozen in liquid nitrogen and stored at −80°C.

Sample aliquots of plasma, urine and peritoneal dialysis fluid were extracted with chloroform/methanol (3/2, vol/vol). After evaporation, the residue was dissolved in 0.1 mol/liter KOH, incubated at 50°C for two hours and, subsequent to neutralization with 0.5 mol/liter HCl, used for determination of total carnitine using an enzymatic assay containing radioisotopic substrate, as described previously [17]. Free carnitine was determined by

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Table 1. Demographic data relating to the study patients/controls

No.	Sex	Age *years*	Height *cm*	Weight *kg*	Time on dialysis, *months*	Diagnosis[a]
1	M	59/58	171/177	64/75	5	Myelomatosis with CRF
2	F	45/46	162/177	64/49	31	CRF uncertain etiology
3	F	52/51	162/160	85/69	4	CRF uncertain etiology
4	M	37/37	192/177	90/77	120	CRF uncertain etiology
5	F	20/20	167/155	79/48	7	Glomerulonephritis
6	F	44/43	157/164	85/60	8	CRF uncertain etiology
7	F	60/59	153/169	57/70	7	Glomerulonephritis
8	M	32/32	180/178	67/85	30	Glomerulonephritis

[a] Abbreviation is chronic renal failure

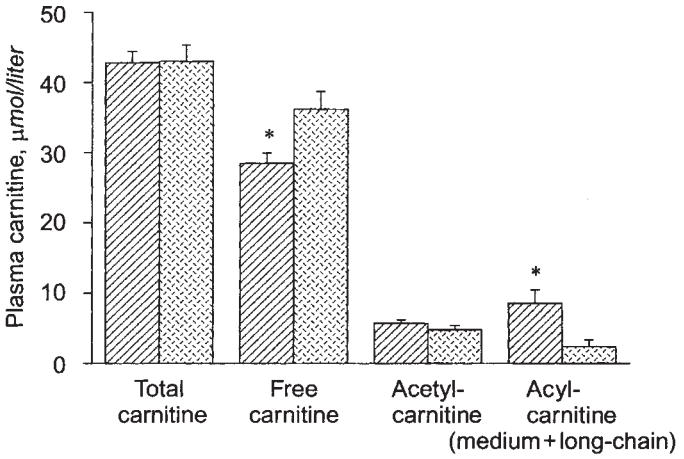

Fig. 1. *Concentrations of total, free, acetyl-, medium- and long-chain acylcarnitine in plasma from continuous ambulatory peritoneal dialysis patients (▨, CAPD) and age- and sex-matched healthy controls (▩).* Values represent means ± SEM. *$P < 0.05$, significantly different from controls.

dissolving the residue in water. Concentrations of acetylcarnitine were measured in 0.5 mol/liter perchloric acid deproteinized plasma, urine and peritoneal dialysis fluid using an enzymatic assay containing radioisotopic substrate, as described previously [18]. All measurements were performed in duplicate. Total acylcarnitine concentrations were obtained by subtracting free carnitine from total carnitine concentrations. Medium- and long-chain acylcarnitine concentrations were obtained by subtracting free carnitine and acetylcarnitine from total carnitine concentrations. The daily loss of free, acetyl, medium- and long-chain acylcarnitine and total carnitine in each CAPD patient was calculated by summing the loss in dialysate and urine. For each control, the daily loss in urine was used. Renal and peritoneal clearances were calculated according to the equation: clearance (ml/min) = [urine or peritoneal dialysis fluid concentration (μmol/liter) * urine or peritoneal dialysis fluid volume (ml)]/[plasma concentration (μmol/liter) * 1440 minutes].

The data were analyzed using Student's unpaired *t*-test (two-tailed). Values in the text and Figures represent means ± SEM.

Results

The plasma total carnitine concentration of CAPD patients was no different from that of controls (42.8 ± 1.6 and 43.1 ± 2.3 μmol/liter, respectively; $P > 0.05$; Fig. 1). However, plasma free carnitine concentration of CAPD patients was significantly lower than that of controls (28.5 ± 1.4 and 36.2 ± 2.5 μmol/liter, respectively; $P < 0.05$; Fig. 1). Though plasma acetylcarnitine concentrations did not differ between the two groups (Fig. 1), this ester represented only 40% of the total plasma esterified carnitine in CAPD patients, but 70% of that in the controls. Comparison of plasma medium- and long-chain acylcarnitine concentration revealed a significantly greater concentration in CAPD patients compared with controls (8.56 ± 1.93 and 2.39 ± 0.93 μmol/liter, respectively; $P = 0.01$; Fig. 1), the excess being of a similar magnitude to the deficit in plasma free carnitine. The total plasma acyl (acetyl-, medium- and long-chain acylcarnitine) to free carnitine ratio was significantly greater in CAPD patients compared with controls (0.52 ± 0.08 and 0.20 ± 0.05, respectively; $P < 0.01$). This was attributable to the lower plasma free carnitine concentration and greater plasma medium- and long-chain carnitine concentration in CAPD patients.

Figure 2 A and B show the renal and peritoneal clearances, respectively, calculated in CAPD patients. Calculations of cumulative (renal + peritoneal) clearances showed comparable total carnitine clearance between the two groups (Fig. 2C). However, the cumulative (renal + peritoneal) free and acetylated carnitine clearances in CAPD patients were greater than the renal clearances in controls ($P < 0.01$; Fig. 2C) and the medium- and long-chain acylcarnitine clearance was lower ($P < 0.01$; Fig. 2C).

Despite the significantly lower daily loss of total carnitine via urine by CAPD patients compared with controls (63.4 ± 17.8 and 240.3 ± 33.0 μmol, respectively; $P < 0.001$; Fig. 3A), the cumulative loss of total carnitine via urine and peritoneal dialysis fluid revealed no significant difference between CAPD patients and controls (269.6 ± 30.0 and 240.3 ± 33.0 μmol, respectively; $P > 0.05$; Fig. 3C). This was mainly attributable to the fivefold greater free carnitine daily loss by CAPD patients via peritoneal dialysis fluid (148.2 ± 18.8 μmol; Fig. 3B) when compared with their corresponding loss via urine (31.7 ± 11.2 μmol; 3A). The loss of free carnitine via peritoneal dialysis fluid was also the main contributor to the significantly greater cumulative loss of free carnitine by CAPD patients when compared with controls (175.8 ± 17.3 and 105.8 ± 16.4 μmol, respectively; $P < 0.05$; Fig. 3C). The ratio of total acylcarnitine to free carnitine in daily combined fluid losses (urine plus peritoneal dialysis fluid) were significantly lower in CAPD patients compared with controls (0.50 ± 0.05 and 1.36 ± 0.14, respectively; $P < 0.001$).

Discussion

The major findings of present study were, firstly, that patients who had undergone CAPD treatment for a mean duration of 27 months have a significantly lower plasma free carnitine concentration compared to a control group matched by age and sex. Most previous studies have shown comparable plasma free carnitine concentrations in CAPD patients [6, 7, 11–13]. Only one previous study has shown a significantly lower plasma free carnitine concentrations in CAPD patients [14]. Secondly, the measurement of daily carnitine loss via analysis of urine and dialysis fluids showed a significantly greater loss of free carnitine and acetylcarnitine in CAPD patients compared with controls. These latter findings were apparent despite the fact that the daily losses of total carnitine of both groups were similar, therefore indicating that a redistribution of carnitine from its free form to an esterified

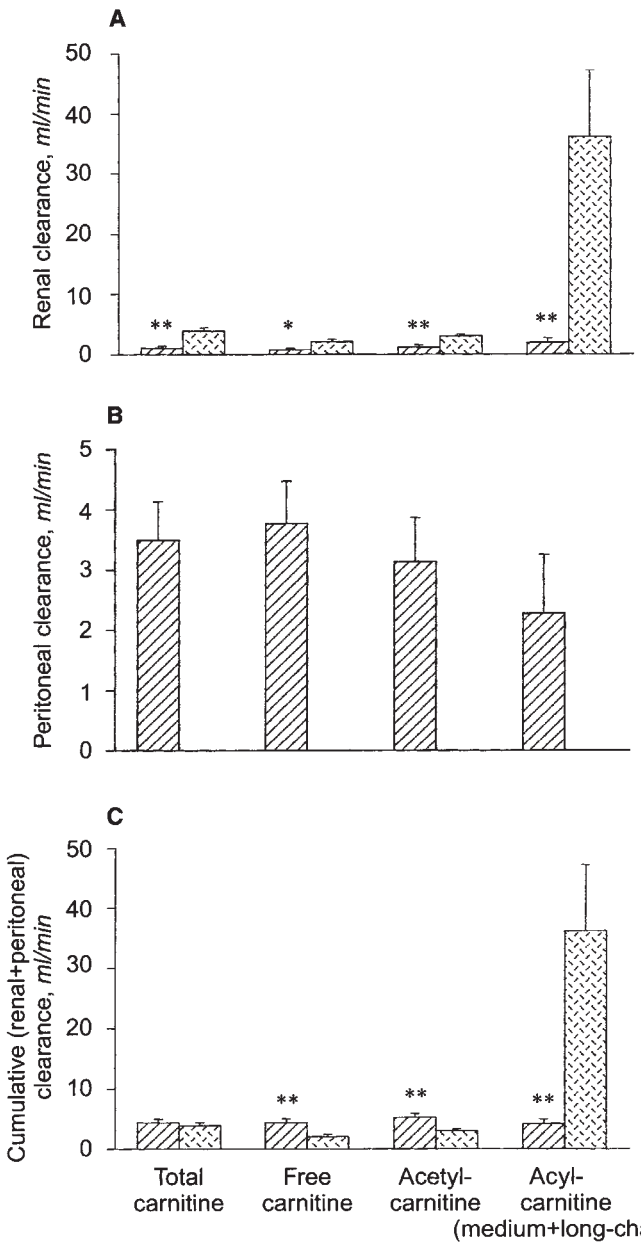

Fig. 2. A. *Renal clearance of total, free, acetyl-, medium- and long-chain acylcarnitine (ml/min) in continuous ambulatory peritoneal dialysis patients (▨, CAPD) and age- and sex-matched healthy controls (▩).* Urine collections were made over 24 hours. Values represent means ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$, significantly different from controls. **B.** Peritoneal clearance of total, free, acetyl-, medium- and long-chain acylcarnitine (ml/min) in continuous ambulatory peritoneal dialysis patients (CAPD). Peritoneal dialysis fluid collections were made over 24 hours. Values represent means ± SEM. **C.** Cumulative (renal+peritoneal) clearances of total, free, acetyl-, medium- and long-chain acylcarnitine (ml/min) in continuous ambulatory peritoneal dialysis patients (CAPD) and age- and sex-matched healthy controls. Urine and peritoneal dialysis fluid collections were made over 24 hours. Values represent means ± SEM. $^{*}P < 0.05$; $^{**}P < 0.01$, significantly different from controls.

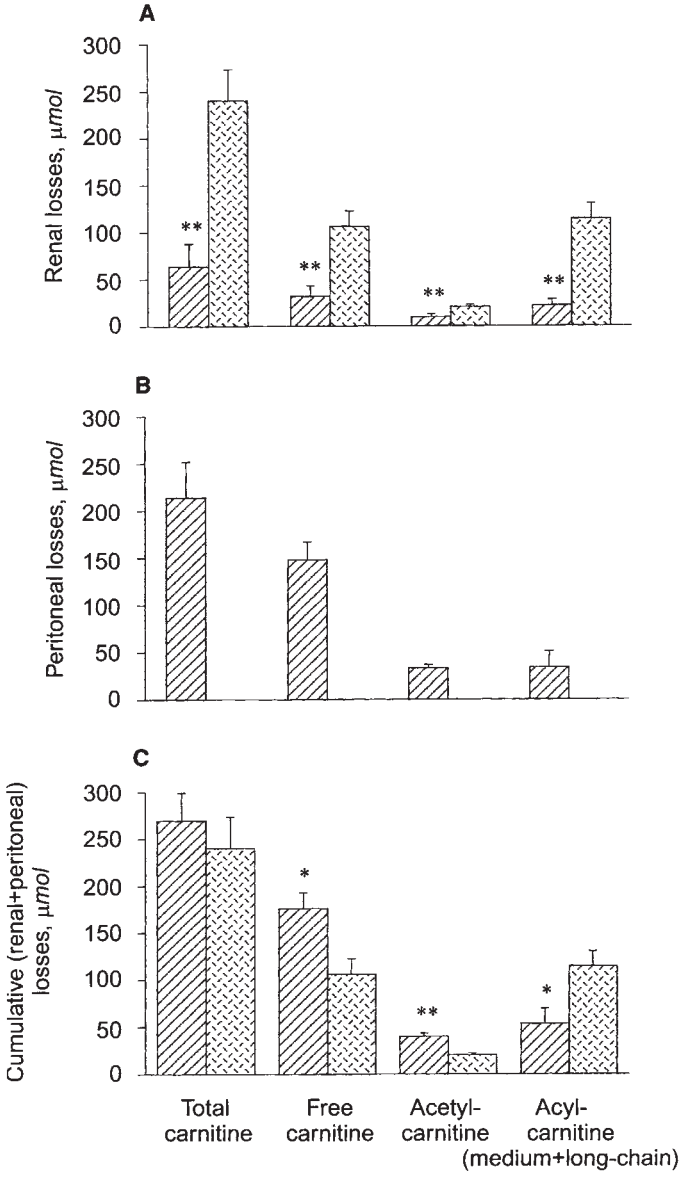

Fig. 3. A. *Daily renal losses of total, free, acetyl-, medium- and long-chain acylcarnitine in continuous ambulatory peritoneal dialysis patients (▨, CAPD) and age- and sex-matched healthy controls (▩).* Values represent means ± SEM. $^{**}P < 0.01$, significantly different from controls. **B.** Daily peritoneal losses of total, free, acetyl-, medium- and long-chain acylcarnitine in continuous ambulatory peritoneal dialysis patients (CAPD). Values represent means ± SEM. **C.** Daily cumulative losses (urine and peritoneal dialysis fluid) of total, free, acetyl-, medium- and long-chain acylcarnitine in continuous ambulatory peritoneal dialysis patients (CAPD) and age- and sex-matched healthy controls. Values represent means ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$, significantly different from controls.

form occurred in the CAPD patients. Thirdly, this redistribution of carnitine in CAPD patients, which has previously been reported [7], was reflected solely by an increase in plasma medium- and long-chain acylcarnitine concentrations.

Carnitine is present in both plasma and urine in free and esterified forms. Plasma free carnitine concentration which is age- and sex-related [15, 16] normally represents 80% of the total carnitine concentration (Fig. 1). The remaining 20% comprise the esterified fraction, of which about ~70% exists in the acetylated form (Fig. 1). However, a redistribution of plasma free carnitine to the esterified form has been reported to occur in disease [19, 20], fasting [21], and during exercise [22]. This is thought to result

from carnitine's ability to buffer increases in tissue acyl group levels [2]. In agreement with this latter function, the present study showed that a similar redistribution of plasma free carnitine into an esterified form occurred in the plasma of CAPD patients. This contributed to a significantly lower free to total carnitine ratio in the plasma of CAPD patients compared with controls (0.67 ± 0.03 and 0.84 ± 0.03, respectively; $P < 0.01$) and to a significantly greater total acyl to free carnitine ratio (0.52 ± 0.08 and 0.20 ± 0.05, respectively; $P < 0.01$). These abnormal ratios have been cited as a possible cause of a "relative carnitine deficiency" [23, 24]. However, the novel finding of the present study was that this redistribution of plasma free carnitine into an esterified form in the CAPD patients was reflected solely by an increase in plasma medium- and long-chain acylcarnitine concentrations (Fig. 1). It is worth mentioning that this change is in contrast to what it is seen in conditions of human ketosis resulted from decreased insulin secretion, where the redistribution is reflected mainly by an increase in short-chain acylcarnitines [20, 21]. Since acetylcarnitine was the major plasma carnitine ester in the control subjects, this change in the profile of plasma carnitine esters in CAPD patients may reflect an impairment of acyl group oxidation occurring in this patient population. Indeed, the intravenous supplementation of plasma with carnitine in hemodialysis patients has been shown to increase markedly not only plasma free carnitine but also total acylcarnitine concentrations, resulting in their ratio continuing to be abnormal [7]. This suggests that there is an excess of acyl groups which are buffered by the administered carnitine. Possible sites for this type of occurrence could be liver where it is thought that an elevation of acyl groups, arising primarily from an impairment of their oxidation, would be buffered by carnitine. It has been suggested that plasma and liver can exchange free carnitine for esterified forms during cellular metabolic stress [22].

There is no evidence to suggest, at least for healthy subjects, that an exchange of esterified carnitine for the free carnitine occurs between skeletal muscle and plasma, as it has been shown that during metabolic stress (muscle contraction) the decline in muscle free carnitine was well matched by similar increases in muscle carnitine esters, mainly acetylcarnitine [3, 22]. Therefore, an alternative explanation for the present findings could be that there was a slower and/or less efficient clearance of medium- and long-chain acylcarnitine by nephrons and/or across the peritoneal cavity in the CAPD patients. It is not completely clear what effect a slower rate of medium- and long-chain acylcarnitine excretion would have upon the metabolism of CAPD patients. Since acylcarnitines and acyl-CoAs are in equilibrium via carnitine acyltransferases [25] an accumulation of the former could serve as a reservoir of acyl groups for acyl-CoA formation. Acyl-CoA compounds, especially long-chain acyl groups, have deleterious effects on cellular membrane integrity due to their detergent properties [26] and have been shown to have an inhibitory effect on adenine nucleotide translocation [27]. These effects may account for some of the pathophysiology of chronic renal failure, including atherosclerotic cardiovascular disorders.

A second aim of the present study was to quantify the daily losses of free and esterified carnitine in CAPD patients. The daily loss of total carnitine measured via analysis of urine and dialysis fluids was not different in CAPD patients when compared with controls (Fig. 3C). However, the daily loss of free carnitine in CAPD patients was 1.7-fold greater than that of controls ($P < 0.05$). The principal route for this increased loss was via peritoneal dialysis fluid, since the magnitude of loss was fivefold greater than that via urine excretion (Fig. 3 A, B). CAPD patients also experienced a significantly greater daily loss of acetylcarnitine (Fig. 3C). However, the increased elimination of free carnitine and acetylcarnitine was matched by a similar decrease in the extent of medium- and long-chain acylcarnitine loss. The ratio of total acylcarnitine to free carnitine in daily fluid losses (urine + peritoneal dialysis fluid) were significantly lower in CAPD patients compared with controls (0.50 ± 0.05 and 1.36 ± 0.14, respectively; $P < 0.001$). These findings could possibly be explained by differences in clearance rates. In controls, the total acylcarnitine renal clearance was eightfold greater than that of free carnitine (16.87 ± 3.88 and 2.15 ± 0.41 ml/min, respectively), which was probably attributable to the preferential renal tubular reabsorbtion of free carnitine. In CAPD patients, however, the cumulative peritoneal and renal clearance of acylcarnitine was similar to that of free carnitine (4.87 ± 0.78 and 4.43 ± 0.63 ml/min, respectively; Fig. 2C). These data also showed that the free carnitine peritoneal clearance (3.77 ± 0.70) was actually greater then the free carnitine renal clearance in controls (2.15 ± 0.41). This may be attributable to a differential loss of the free form across the peritoneal cavity resulting from the more rapid diffusion of small molecules like free and acetylcarnitine. It has previously been shown that endogenous medium size molecules (350 to 2,000 Daltons) are more efficiently transferred during CAPD than during other forms of dialysis treatment [28].

Although the daily acetylcarnitine losses by CAPD patients were significantly greater than by controls (Fig. 3C), the respective plasma levels differed only slightly (Fig. 1) and it seems unlikely that the greater daily losses were directly harmful. However, because of the potential deleterious effects of long-chain acyl-CoA accumulation discussed previously, it may be of more metabolic significance that the plasma level of medium- and long-chain acylcarnitine of CAPD patients was three times greater than that of controls (Fig. 1).

In conclusion, the present results demonstrate that the plasma total carnitine concentration and the daily loss of total carnitine were similar when comparing CAPD patients with age- and sex-matched controls. However, the plasma concentration of free carnitine was lower in CAPD patients than in controls and, conversely, the daily loss of free carnitine was greater. The ratio of total acylcarnitine to free carnitine was significantly greater in plasma of CAPD patients than in controls and lower in daily fluid losses. These ratio differences may have resulted from an exchange of plasma free carnitine with hepatic medium- and long-chain acylcarnitines and/or to a differential loss of free carnitine and acylcarnitine across the peritoneal cavity. Finally, given the likely rise in the concentration of plasma medium- and long-chain acylcarnitines as a result of carnitine therapy [7], our observations suggest a need for some caution in the use of carnitine supplementation in CAPD patients, until more is known of the metabolic consequences relating to the accumulation of these compounds.

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