Absolute and Relative Carnitine Deficiency in Patients on Hemodialysis and Peritoneal Dialysis

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Introduction. Carnitine deficiency is commonly seen in dialysis patients. This study assessed the association dialysis and pediatric patients' characteristics with plasma carnitines levels.
Materials and Methods. Plasma carnitine concentrations were measured by tandem mass spectrometry in 46 children on hemodialysis or peritoneal dialysis. The total carnitine, free carnitine (FC), and L-acyl carnitine (AC) levels of 40 µmol/L and less, less than 7 µmol/L, and less than 15 µmol/L were defined low, respectively. An FC less than 20 µmol/L and an AC/FC ratio greater than 0.4 were considered as absolute and relative carnitine deficiencies. The correlation between carnitines levels and AC/FC ratio and age, duration of dialysis, characteristics of dialysis, and blood urea nitrogen and serum albumin concentrations were assessed.
Results. Absolute carnitine deficiency, low total carnitine, and low AC concentrations were found in 66.7%, 82.6%, and 51% of the patients, respectively. All of the patients had relative carnitine deficiency. Carnitine measurements were not significantly different between the hemodialysis and peritoneal dialysis groups. More severe relative carnitine deficiency was found in those with lower blood urea nitrogen levels and those on peritoneal dialysis. No linear correlation was found between carnitine levels and age, duration of dialysis, characteristics of dialysis, serum albumin level, or blood urea nitrogen level.
Conclusions. Absolute and relative carnitine deficiencies are common among children on dialysis. Patients with lower blood urea nitrogen levels and peritoneal dialysis patients are more prone to severe relative carnitine deficiency.

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INTRODUCTION

Free carnitine (FC) and acyl carnitine (AC) formed during cell metabolic processes are localized in the mitochondria, peroxisomes, endoplasmic reticulum, and nucleus.[1] Carnitine is available from the diet, the major sources being red meats and dairy products. It is synthesized endogenously by the muscles, liver, kidney, and brain. Carnitine is filtered readily by the glomerulus and 90% of the filtrated load is reabsorbed in the proximal tubule.[2] Plasma and tissue carnitine levels are maintained by absorption from the gastrointestinal

tract, endogenous synthesis, and carrier-mediated renal tubular reabsorption. The kidney has an important role in maintaining normal levels of FC and removing the excess short-chain acyl groups.[3] Carnitine deficiency is commonly seen in dialysis patients and is responsible for symptoms of anemia, cardiomyopathy, and muscle weakness.[4] The criteria for diagnosis of carnitine deficiency are a serum FC level less than 20 µmol/L (absolute deficiency) or a serum AC/FC ratio greater than 0.4 (relative deficiency).[5]

This study aimed to define the prevalence of carnitine deficiency in dialysis patients and to correlate the results with age, sex, dialysis modality, duration of dialysis, dialysis characteristics, serum albumin, blood urea nitrogen (BUN) levels, and presence or absence of residual renal function (RRF). The clinical effects of carnitine deficiency such as cardiomyopathy, anemia, and muscle weakness were not considered in the study.

MATERIALS AND METHODS

Pediatric patients on maintenance hemodialysis and peritoneal dialysis were recruited to measure plasma carnitine concentrations (total carnitine [TC], FC, and AC). Those who were receiving medications with an effect on plasma carnitine levels (such as sodium valproate) were excluded from study. Written consent was obtained from the patients and their parents. The study was funded by a research grant from the research and development section of Mashhad University of Medical Sciences and its protocol was approved by the local ethics committee.

In the hemodialysis patients, the types of the dialysis membrane were low-flux dialyzer R3-R5 and low-flux polysulfone membranes. The blood flow rates were regulated on 100 mL/min to 300 mL/min, depending on the weight. In the patients on continuous peritoneal dialysis (CAPD), dialysis I solution was routinely administrated.

Blood samples were obtained in the fasting condition and before dialysis in the hemodialysis patients. Plasma carnitine concentration was determined by an tandem mass spectrometry kit for amino acids and acylcarnitine (Neogram, PerkinElmer Life and Analytical Sciences, Turku, Finland). The kit had the capability to measure over 40 analytes, even though it was supplied with 23 internal standards and 21 controls. The measurement of FC and AC involved extraction of dried blood spots with a solution containing stable isotope labeled internal standards and analysis using a tandem mass spectrometry (MS/MS) system. The normal range was defined as 43.2 µmol/L to 55.9 µmol/L for TC,[6] and a plasma TC concentration of 40 µmol/L and less was considered deficiency.[7] According to the kit characteristics, normal values for FC and AC were defined as 7 µmol/L to 45 µmol/L, and greater than 15 µmol/L, respectively, and plasma levels less than 7 µmol/L and less than 15 µmol/L were defined low values, respectively. Relative carnitine deficiency was considered a plasma AC/FC ratio greater than 0.4 and absolute carnitine deficiency as a serum FC less than 20 µmol/L.[5] To define the severity of functional carnitine deficiency, ratios of 0.41 to 0.99 were considered as mild to moderate and amounts of 1 and greater were defined as severe functional carnitine deficiency. Severity of functional carnitine deficiency was compared based on clinical and biochemical characteristics of the cases.

Normality of distribution of quantitative variables were checked by the 1-sample Kolmogorov-Smirnov test. Correlation between plasma carnitine concentrations with different variables were analyzed using the Pearson correlation test. Correlation defined significant at the 0.01 level ($r > 0.01$, $P < .05$). The chi-square and the independent *t* tests were used for univariable analyses, and if needed, a logistic regression model was built for multivariable analysis. *P* values less than .05 were considered significant.

RESULTS

Characteristics of the 46 participants are summarized in Table 1. The mean carnitine concentrations were reported to be 35.5 ± 14.9 µmol/L (range, 18.1 µmol/L to 82.4 µmol/L) for TC, 19.4 ± 10.0 µmol/L (range, 8.2 µmol/L to 48.9 µmol/L) for FC, and 16.0 ± 5.5 µmol/L (range, 7.9 µmol/L to 34.8 µmol/L) for AC. The mean AC/FC ratio was 0.90 ± 0.25 (range, 0.53 µmol/L to 1.6 µmol/L). Plasma FC concentrations were greater than 7 µmol/L in all of the children, but absolute carnitine deficiency (FC < 20 µmol/L) was detected in 32 (66.7%). Deficiencies of TC and AC were documented in 38 (82.6%) and 24 (51%) children, and relative carnitine deficiency (AC/

Table 1. Characteristics of the Children on Dialysis*

Characteristic	Value
Age, mo	
All	162 ± 77.4
Patients on peritoneal dialysis	77.0 ± 49.5
Patients on hemodialysis	199.5 ± 54.4
Dialysis modality	
Hemodialysis	27 (58.7)
Continuous Ambulatory peritoneal dialysis	13 (28.3)
Both modalities in separate times	6 (13.0)
Sex	
Male	27 (58.7)
Female	19 (41.3)
Months since onset of dialysis	
All	43.8 ± 31.0
Patients on peritoneal dialysis	43.4 ± 33.0
Patients on hemodialysis	33.0 ± 16.0
Etiologies of chronic kidney disease	
Vesicoureteral reflux with or without renal dysplasia	20 (42.6)
Chronic glomerulonephritis	3 (6.4)
Rapidly progressive glomerulonephritis	1 (2.1)
Childhood nephrotic syndrome	4 (8.5)
Infantile nephrotic syndrome	1 (2.1)
Neurogenic bladder	5 (10.6)
Polycystic kidney diseases	2 (4.3)
Urinary calculus	2 (4.3)
Familial juvenile nephronophtisis	1 (2.1)
Cystinosis	1 (2.1)
Idiopathic	6 (14.9)
Characteristics of dialysis cycles in peritoneal dialysis	
Dwelling volume, mL/kg	40.3 ± 15.8
Dwelling time, h	3.4 ± 0.9
Number of cycles during a day	4.8 ± 0.5
Volumes of cycles during a day, mL/kg	188.4 ± 89.7
Hours of dialysis per week in hemodialysis patients	
4 hours, 3 times per week	19 (70.4)
< 12 hours per week)	6 (22.2)
Dialysis >12 hours per week	2 (7.4)
Hours of dialysis per week	10.1 ± 3.1
Urine output	
Anuria	11 (23.9)
3 times in 24 hours	21 (45.7)
3 time in 24 hours or more	6 (13)
Undetermined	8 (17.4)
Supplementation with oral carnitine	
No supplement	24 (52.2)
Receiving oral supplement (250 g/d to 500 g/d)	22 (47.8)
Previous transplantation	9 (19.6)

*Values are mean ± standard deviation or count (percentage).

FC > 0.4) was noted in all.

Deficiency of AC was as common in the boys as in the girls (P = .96). There were no significant differences between groups in terms of total volumes of cycles per day in CAPD patients and hours of dialysis per week in hemodialysis patients, serum BUN, and albumin levels. Two-thirds of hemodialysis and 38.5% of CAPD patients were AC deficient (P = .04; Table 2).

The mean concentrations of AC, TC, and FC and the AC/FC ratio were not significantly different in terms of dialysis modality or presence or absence of RRF (Tables 3 and 4). Although severe relative carnitine deficiency (AC/FC > 1) was more prevalent in the CAPD children (44% versus 22% in hemodialysis patients), the difference was not significant (P = .50; Table 5). Patients with lower serum BUN concentrations were more likely to have severe relative carnitine deficiency (P = .04; Table 6), but there was not any positive correlation between serum BUN concentrations and severity of relative carnitine deficiency. We did not find any linear correlation of plasma TC, FC, or AC concentrations, or AC/FC ratios with age, duration of dialysis, dialysis characteristics, and serum BUN and albumin levels (Table 6).

DISCUSSION

Plasma TC is considered low when it is less than 20 µmol/L. In our series, only 2 children (4.3%) had low TC. Plasma concentration of FC is in dynamic balance with that of AC, the AC/FC ratio, is considered normal when it is less than 0.25 to 0.4.[8,9] Deficiency of FC results in an abnormally elevated AC/FC ratio.[9] In healthy adults, FC comprises more than 88% of the TC (12% esterified), whereas in patients with end-stage renal disease, it accounts for 67% of the TC (33% esterified).[10] In our series, FC accounted for 45% to 59% of TC (41% to 55% esterified).

A positive correlation between TC and FC plasma concentrations and the age has been reported in healthy children. From the second year of life until adulthood, no change in plasma carnitines concentration is noted, and after 17 years of age, no differences are seen between male and female individuals.[11] Osorio and coworkers performed a study on healthy children for establishing AC reference values.[12] They divided children by age into those < 1 month old; 1 to 12 months old; 1 to 7 years old, and 7 to 18 years old. No significant differences were found in relation to age or sex, whereas another study revealed that plasma FC

Table 2. Characteristics of Children With Carnitine Deficiency and Those without Carnitine Deficiency

Characteristic	Children on Dialysis		*P*
	Normal Acyl Carnitine Concentration	Acyl Carnitine Deficiency	
Age, mo	143.6 ± 90.5	175.8 ± 61.1	.16
Sex			
Male	13	14	
Female	9	10	.96
Dialysis modality			
Hemodialysis	9	18	
Peritoneal dialysis	8	5	.04
Months since onset of dialysis	47.5 ± 32.8	36.7 ± 24.8	.23
Hours of hemodialysis per week	10.2 ± 3.3	10.1 ± 3.0	.89
Peritoneal dialysis volume per day	183 ± 72	197 ± 93	.78
Blood urea nitrogen, mg/dL	52.4 ± 22.6	60.0 ± 11.0	.23
Serum albumin, g/dL	3.4 ± 0.6	3.4 ± 0.4	.85

Table 3. Plasma Carnitine Status in Children on Hemodialysis and Peritoneal Dialysis

Plasma Carnitine Measurements	Children on Peritoneal Dialysis	Children on Hemodialysis	*P*
Acyl carnitine-free carnitine ratio	2.00 ± 1.00	2.40 ± 3.84	.50
Total carnitine, μmol/L	39.0 ± 15.5	34.7 ± 15.6	.42
Acyl carnitine, μmol/L	17.9 ± 5.8	14.9 ± 5.5	.11
Free carnitine, μmol/L	20.9 ± 10.2	19.7 ± 10.6	.74

Table 4. Plasma Carnitine Status in Children With and Without Residual Renal Function

Plasma Carnitine Measurements	Children Without Residual Renal Function	Children With Residual Renal Function	*P*
Acyl carnitine-free carnitine ratio	2	2	> .99
Total carnitine, μmol/L	28.9 ± 5.0	35.2 ± 13.9	.13
Acyl carnitine, μmol/L	13.7 ± 2.9	16.3 ± 5.4	.12
Free carnitine, μmol/L	15.2 ± 3.8	18.8 ± 9.1	.19

Table 5. Severity of Relative Carnitine Deficiency by Patients' Characteristics

Characteristic	Acyl Carnitine-Free Carnitine Ratio		*P*
	< 1	≥ 1	
Age, mo	171.5 ± 69.5	135.2 ± 90.9	.15
Sex (%)			
Male	19 (41.3)	8 (17.4)	
Female	13 (28.3)	6 (13.0)	.89
Dialysis modality (%)			
Hemodialysis	21 (52.5)	6 (15.0)	
Peritoneal dialysis	9 (22.5)	4 (10.0)	.42
Months since onset of dialysis	38.8 ± 25.1	48.7 ± 36.3	.31
Hours of hemodialysis per week	10.0 ± 3.2	10.6 ± 2.9	.68
Peritoneal dialysis volume per day	188.6 ± 120.7	188.1 ± 41.7	.99
Blood urea nitrogen, mg/dL	60.4 ± 15.7	47.2 ± 20.8	.04
Serum albumin, g/dL	3.5 ± 0.6	3.3 ± 0.3	.27

and TC levels correlated with sex and age in healthy adults.[13]

In an extended study, plasma FC and AC levels were evaluated in healthy Japanese males and females aged less than 1 to 65 years.[14] The researchers noted that serum FC increased with age in children of both sexes and plasma FC level was related to age and sex, while serum AC level remained constant. Age-dependent variations in FC and AC concentrations have been reported by other studies.[15] In our series, which included children and young adults, no positive

Table 6. Correlations Between Plasma Carnitine Concentrations and Patients' and Dialysis Characteristics

Variable	Total Carnitine		Free Carnitine		Acyl Carnitine		Acyl Carnitine-Free Carnitine Ratio	
	r	*P*	r	*P*	r	*P*	r	*P*
Age	-0.069	.65	0.050	.96	-0.187	.21	-0.298	.04
Duration of dialysis	-0.077	.63	-0.125	.43	0.037	.82	0.184	.24
Hours of hemodialysis per week	0.149	.46	0.174	.39	0.075	.71	-0.155	.18
Total volumes of peritoneal dialysis cycles per day	-0.236	.36	-0.191	.46	-0.273	.29	-0.018	.95
Blood urea nitrogen	-0.062	.72	-0.012	.95	-0.148	.40	-0.190	.28
Serum albumin	0.265	.21	0.305	.15	0.179	.40	-0.279	.19

correlation was noted between age with TC, FC, and AC concentrations. Carnitine is a hydrophilic low molecular weight substance that can easily be lost during hemodialysis. Reduced serum carnitine level has been observed in patients on chronic hemodialysis before and after dialysis. The reduced carnitine level in plasma might lead to a similar reduction in the carnitine level in the tissues which potentially can interfere with fatty acid metabolism in the cells and contribute to weakness which patients experience within the first few hours postdialysis.[16]

Niacin, vitamin B6, vitamin C, and iron are required as cofactors for endogenous carnitine production. Deficiencies of lysine, methionine, vitamin C, vitamin B6, and iron have all been reported to lead to reduced fluid and tissue levels of carnitine.[17] Healthy children and adults do not need to receive carnitine from food or supplements due to endogenous production.[18-20] Based on the Food and Nutrition Board of the National Academies, carnitine is not an essential nutrient, and no recommended dietary allowance is established for carnitine.[20,21]

In dialysis patients, FC is lower and AC is higher than those of the general population. This shift may be attributable to loss of renal parenchyma, poor clearances, and poor dietary intake.[7] In contrast to our findings, it has been suggested that end-stage renal disease leads to increased esterified fraction of L-carnitine and chronic hemodialysis results to gradual removal of FC.[6] All of our hemodialysis cases had normal FC, whereas the majority were AC deficient.

Few studies have focused on serum carnitine concentration in PD patients.[7,14,22] Pliakogiannis and colleagues[22] evaluated the influence of serum carnitine levels on the metabolic status and lipid profile of 22 patients on CAPD. They found that the mean serum TC was normal and FC was reduced, while AC was elevated. Evaluation of serum carnitine levels in our CAPD children revealed AC deficiency in 38.5%, low serum TC in 69.2%, normal FC in all, and FC levels less than 20 µmol/L (absolute carnitine deficiency) in 61.5%. A study in India reported carnitine deficiency in 68.4% and 64.3% of PD and hemodialysis patients, respectively.[7] They found that carnitine levels in the hemodialysis group correlated positively with the presence of diabetes mellitus and hypertension. No association of carnitine level with RRF and the diet (vegan or nonvegan diet) was found. We did not measure RRF in our series, but comparing mean concentrations of AC, TC, and FC in anuria (no RRF) and nonanuria cases (patients with different amounts of RRF), there was no significant differences.

Available data indicate that the FC levels are typically normal in PD patients.[7] Similar to Ramalakshmi and colleagues' findings,[7] our data showed that carnitine deficiency was common in PD patients; there are no association between carnitine level and dialysis duration or serum albumin levels. In contrast to their study, in our patients, carnitine deficiency was significantly more prevalent in hemodialysis than in CAPD patients. It should be emphasized that it is not sufficient to focus solely on L-carnitine levels in plasma because plasma levels may not give a true reflection of tissue content.[10] The reduction in plasma L-carnitine levels occurs within the first few months of dialysis. In patients on hemodialysis, plasma and muscle carnitine levels fall immediately after the dialysis, whereas the levels remain in the normal range in patients on intermittent PD and CAPD.[23] The recommended dietary restrictions are not so strict in CAPD compared with hemodialysis, and the majority of PD centers encourage increased

intake of biologically active proteins in PD patients to reduce the risk of hypoalbuminemia and replace amino acid losses by dialysis; thus, it is expected that CAPD patients have significantly lower metabolic derangements including carnitines deficiency, but results of our study did not confirm this idea.

In hemodialysis patients, increased hours of dialysis per week can result in several metabolic derangements. Nocturnal hemodialysis includes of 5 to 6 sessions per week, 8 hours per treatment, while standard hemodialysis consists of 3 four-hour sessions per week. Hothi and coworkers[9] reported decreased plasma FC and AC concentrations, and improvement in AC/FC ratio by conversion from standard to nocturnal hemodialysis. Comparing means plasma carnitines concentrations and AC/FC ratio between children on standard hemodialysis and those who received a dialysis dose less than 12 hours per week revealed no meaningful differences.

Kokot and colleagues[24] found carnitine deficiency in 22.7% of their hemodialysis cases. In our series, two-thirds of hemodialysis and 38.5% of CAPD patients had AC deficiency and all had relative carnitine deficiency with no significant difference in severity of relative carnitine deficiency based on modality of dialysis. Serum carnitine accounts for 0.5% of total body carnitine. Although dietary sources account for 75% of carnitine turnover, carnitine-restricted diets have little impact on total body carnitine because of renal conservation.[25] A wide range of values have been reported for serum carnitine levels in normal population, with mean concentrations of FC for males being 50.4 ± 7.6 μmol/L and for females being 40.2 ± 7.2 μmol/L.[14,26] In the group of patients aged 15 to 50 years, the mean FC in males was significantly higher than that in females, while serum AC remained constant. Renal reabsorption of FC showed no age- and sex-related differences.[14]

Serum carnitine assessment in children has been shown a positive correlation between TC and FC plasma concentrations and age. Both FC and AC concentrations are elevated on the first days of life. Then, it decreases and subsequently increases during the first years of life. From the second year of life until adulthood, the serum carnitine concentration is steady, and up to 17 years of age, no differences is seen between sexes.[11]

Evans[27] reported the temporal changes in the level and composition of carnitines before and after hemodialysis. The author found that the plasma non-acetyl acyl carnitine levels increased with a longer duration of dialysis. The highest concentrations of L-carnitine are found in red meat and dairy products.[2] In hemodialysis patients, a decrease intake of red meat and dairy products is routinely recommended to prevent severe uremia and hyperphosphatemia, thus hemodialysis usually have low carnitine diets. No restriction in protein intake is recommended in CAPD, but as phosphate is poorly removed by peritoneal dialysis, majority of patients (except infants) have restricted intake of dairy products. A decrease in both FC and AC concentration in uremic patients, 6 months after onset of dialysis, is a common finding. Hemodialysis patients have low plasma carnitine concentrations, despite a diet with normal carnitine intake and a loss during dialysis lower than the loss of normal subjects through urinary excretion.[28]

In patients receiving maintenance hemodialysis, serum levels of FC are subnormal,[29,30] whereas concentrations of esters are elevated. Low FC levels have also been observed in skeletal muscle and tend to decrease proportionally to the duration of dialysis.[31] Pablo and colleagues[18] reported no significant difference between the mean carnitine levels in CAPD patients with controls, whereas other studies reported near normal or decreased plasma concentration of TC, with an abnormal carnitine fraction profile in CAPD patients.[22] Clinical practice guidelines for the treatment of chronically uremic patients suggest that there are insufficient data to support the routine use of carnitine in dialysis patients.[32,33]

Although, the role of iron deficiency as a cause of secondary carnitine deficiency is not well defined, a few studies have reported significantly lower serum carnitines concentrations in iron-deficient versus healthy children.[34] In our cases, the mean serum iron levels in those with absolute carnitine deficiency were not significantly different from those without it.

Transferrin saturation is a marker of iron available for hemoglobin synthesis with a therapeutic target greater than 20% in chronic kidney disease patients.[35] We compared FC concentrations in iron-deficient children (transferrin saturation < 20%) with those who had normal iron stores (transferrin saturation ≥ 20%) and found no significant differences. In addition, no significant difference

was found in transferrin saturation between those with absolute carnitine deficiency compared with those without it.

CONCLUSIONS

We found that absolute and relative carnitine deficiencies are common in dialysis patients. It seems that children with lower serum BUN levels (which indicates deficient protein intake) and CAPD children are more prone to have more severe relative carnitine deficiency. In addition, there are no correlations between carnitine concentrations and age, sex, serum BUN and albumin, or dialysis characteristics. Clinical impacts of absolute and relative carnitine deficiencies on muscles performance, cardiac function (mainly cardiac output, exercise tolerance, and finally outcome) are important clinical points that should be considered in future research.

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CONFLICT OF INTEREST

None declared.

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