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Low Plasma Carnitine in Patients on Prolonged Total Parenteral Nutrition: Association with Low Plasma Lysine

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ABSTRACT. Plasma carnitine levels were determined in 17 patients maintained on long-term total parenteral nutrition (TPN) for a mean (±SEM) period of 69 ± 11 months (range 12–196). All had severe malabsorption and were dependent on intravenous feeding. Plasma carnitine was determined by a modified Cederblad enzymatic method. Mean plasma carnitine was significantly below the mean normal for females ($p < 0.02$) and borderline low for males ($p = 0.07$). In six patients the levels were below the low normal range, and in five others they were at the lowest levels of normal. Of the six patients with normal levels, three had elevated serum creatinine, indicating renal dysfunction which may by itself elevate plasma carnitine. In 10 patients the plasma levels of lysine (a carnitine precursor) were determined and found to be lower than normal ($p < 0.05$). Plasma carnitine levels correlated positively with serum albumin ($r = 0.62$, $p < 0.05$), and negatively with serum alkaline phosphatase ($r = -0.64$, $p < 0.05$). Thus, patients maintained on long-term TPN may have low plasma carnitine, which could represent carnitine deficiency. The low plasma carinitine may be related to a deficiency of the carnitine precursor lysine. Further studies are required to determine the significance of the low plasma carnitine and whether carnitine supplementation should be required in long-term TPN. (*Journal of Parenteral and Enteral Nutrition* **14**:255–258, 1990)

Carnitine is a quaternary amine which plays an essential role in the transfer of long-chain fatty acids into the mitochondria for subsequent oxidation and ATP production.[1] In normal humans carnitine is either synthesized in the liver and kidneys (from lysine and methionine) or absorbed from the gastrointestinal tract.[2] Foods with high carnitine content include red meat, eggs, and dairy products. The relative contributions of endogenous and exogenous carnitine in the normal physiological state have not been elucidated.

Primary carnitine deficiency occurs because of a genetic disorder.[3] Secondary or acquired carnitine deficiency has been reported in cirrhosis,[4] in renal failure,[5] and in patients receiving TPN.[6,7]

Manifestations of carnitine deficiency include liver dysfunction and steatosis, progressive myopathy and episodes of hypoglycemia.[2,3] Liver dysfunction occurs in patients receiving TPN and is characterized histologically by steatosis and cholestasis.[8–15] It is not known whether the TPN-induced liver function abnormalities are related to carnitine deficiency.

Patients on prolonged TPN are deprived of exogenous carnitine because of malabsorption, therefore, they depend only on endogenous production. TPN solutions contain the precursor amino acids of carnitine, lysine and methionine; however, it has been shown that intravenous methionine is not as effective as enterally absorbed methionine for the transsulfuration pathway[16] which leads to carnitine synthesis. Surgical patients receiving TPN were shown to develop a progressive decrease in plasma carnitine levels within 20 to 40 days.[6] Low circulating levels of carnitine were also noted in patients on home TPN.[7] We determined the plasma carnitine in our home TPN patients and correlated the findings with liver function. We also measured and correlated the plasma lysine and methionine levels with those of carnitine.

METHODS

Patients

Seventeen patients were investigated. The clinical details, underlying diseases, and duration of TPN therapy are outlined in Table I. All patients had severe intestinal malabsorption, verified by the nature of their intestinal diseases, resections, and/or radiation effect, and by one or more absorption tests (D - xylose, ^{14}C-tripalmitate, 3-days fat absorption and the Schilling test). All patients depended on TPN for their nutritional requirements.

TPN Solutions

Composition of the TPN solutions is outlined in Table II. These solutions were usually infused over a 10- to 12-hr period during the night. Some of the patients had minimal amounts of oral intake. The absorption from oral intake was small because of documented severe malabsorption.

Laboratory Methods

Blood samples for determination of plasma carnitine levels were drawn 4 hr after completing infusion of TPN solutions. The samples were taken in EDTA-containing tubes and after separation the plasma was frozen until

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TABLE I
Data on individuals in the survey

Primary diagnosis	Age/sex	Length of TPN therapy (months)
Patients with radiation enteritis		
Lymphoma/short bowel syndrome	51/F	80
Gastric leiomyosarcoma	65/F	85
Embryonal rhabdomyosarcoma	27/M	47
Embryonal rhabdomyosarcoma	22/M	101
Testicular carcinoma	44/M	157
Wilm's tumor	40/F	36
Cervical carcinoma	49/F	89
Patients with short bowel/(length*)		
Intestinal pseudo-obstruction/60 cm	51/M	112
Intestinal pseudo-obstruction/30 cm	22/M	57
Intestinal malrotation/0 cm	32/F	22
Intestinal infarction/15 cm	68/F	80
Intestinal infarction/43 cm	55/M	48
Intestinal infarction/24 cm	56/F	24
Patients with inflammatory bowel diseases		
Collageous sprue/malabsorption	31/M	12
Crohn's disease, multiple fistulas	43/M	36
Crohn's disease, multiple fistulas	44/F	84
Crohn's, short bowel	64/M	70

* Of remaining jejuno-ileum.

TABLE II
Composition of daily TPN solutions

Nutrient	Intake
Amino acids*	1–1.25 g/kg body weight
kCalories (nonprotein)	1647 ± 391 (1000–2600)
Lipid fraction of calories	21 ± 12% (8–50%)
Fluids	1000–2000 ml
Na	1–2 mEq/kg
K	1 mEq/kg
Ca	270–360 mg
P	450–900 mg
Zn	5–8 mg
Cu	0.2–0.4 mg
Se	20–40 μg
Cr	10–20 μg
Mn	0.1 mg
Vitamins	MVI12
Lysine	3–5 g
Methionine	2–4 g

* Amino acid solution: Travasol.

time of analysis. The Cederblad enzymatic method with isotope tracer[17] was used to determine the plasma carnitine levels. Blood samples were taken simultaneously for routine laboratory determination of bilirubin, creatinine, alkaline phosphatase, SGOT, and albumin. Plasma methionine and lysine were determined using high pressure liquid chromatography (Pickering Laboratories, Mountain View, CA).

Statistical Analysis

Values for normal plasma carnitine levels were used from a recent report which utilized 890 blood samples taken from Red Cross blood donors.[18] The method of determination of the plasma carnitine levels in that report is identical to our method. All data were put on a data base diskette. Mean, standard error of the mean, and correlation coefficients were calculated on "minitab" software.[19] Multiple regression analysis was performed on the same system. Nonparametric analysis was done using 2 × 2 frequency tables for the normal and abnormal results, and independent events were determined according to the Fisher's exact test using reference tables.[20]

RESULTS

The plasma carnitine, creatinine, and results of liver function tests are listed in Table III for all the study subjects.

The mean serum carnitine for the eight females was 33.9 ± 5.2 nmol/ml, significantly below the mean of 50.3 ± 11.8 nmol/ml in normals of the same age group ($p < 0.02$). The mean plasma carnitine in the nine males was 39.9 ± 5.7 nmol/ml compared to 51.7 ± 10.8 nmol/ml in normals ($p = 0.07$). In six patients (8, 9, 10, 11, 14, 17) the levels (adjusted for sex and age group) were below the normal range and in five others (1, 2, 4, 6, 16) they were just in the lowest levels of the normal range. In the remaining six patients the plasma carnitine was within the normal range. Three of these six patients (3, 5, 7, 12, 13, 15) had renal failure, which is known to elevate the plasma carnitine, since carnitine is excreted through the urine[5] and accumulates during renal failure. Indeed, there was a significant positive correlation between the plasma carnitine and serum creatinine for the whole group ($r = 0.56$ $p < 0.05$).

As can be seen from Table III, the liver function tests demonstrated mild hepatic dysfunction in all patients except patient no. 10, who at the time of the study had severe liver dysfunction secondary to acute non-A non-B hepatitis which subsequently subsided. There was a significant negative correlation between the plasma carnitine and the serum alkaline phosphatase ($r = -0.64$ $p < 0.02$) and a positive correlation between the plasma carnitine and the serum albumin ($r = 0.62$ $p < 0.02$).

Stratification by the length of remaining small bowel showed that the six patients with less than 2 feet of small bowel had a mean plasma carnitine of 32 ± 8 nmol/ml, while the 11 patients with more than 2 feet had a mean of 40 ± 5, not significantly different. The duration of home TPN therapy also did not correlate with the plasma carnitine.

In order to assess the possibility of carnitine precursors deficiency, the plasma content of lysine and methionine was determined in nine of the 17 patients using the same plasma samples used for carnitine determination. The individual levels are outlined in Table IV. The mean value for venous plasma lysine was 142 ± 5 nmol/ml, significantly lower than the mean of 245 ± 12 nmol/ml for normals determined in our laboratory ($p < 0.005$). The plasma lysine levels in our patients was also below the mean normal ($p < 0.0005$) reported by Halmi et al[21] using the same methods. There was a significant correlation between the plasma carnitine and lysine ($r = 0.45$, $p < 0.05$).

Significant negative correlation was found in the same nine patients between the methionine and lysine levels, with $r = -0.36$ $p < 0.05$.

TABLE III
Plasma carnitine and results of kidney and liver function tests

Patient No./sex	Plasma carnitine (nmol/ml)	Serum creatinine (mg/dl)	Serum (IU/liter)	Alk. Phos. (IU/liter)	Serum	Serum bilirubin (g/dl)	Blood albumin glucose (mg/dl)
1/F	29.8	1.4	214	34	1.1	3.4	92
2/F	34.9	0.6	114	36	0.6	3.7	107
3/M	70.7	4.4	92	48	0.9	4.4	92
4/M	33.6	1.2	102	36	0.3	3.4	78
5/M	45.9	2.0	97	23	0.6	4.0	100
6/F	35.3	2.6	133	41	0.5	3.9	82
7/F	63.1	1.5	78	23	0.3	4.2	101
8/M	27.7	1.2	72	16	0.5	3.8	135
9/M	28.3	0.5	242	35	0.2	3.9	93
10/F	10.9	0.7	414	360	14.8	3.3	75
11/F	25	0.8	126	28	0.5	3.9	101
12/M	62.9	1.0	76	19	0.8	4.1	102
13/F	37	0.9	142	38	0.2	3.4	118
14/M	24.5	1.5	172	35	0.7	3.8	88
15/M	41.4	1.0	94	23	0.7	3.5	104
16/F	35.2	1.2	161	33	0.5	4.2	101
17/F	24.2	1.3	129	45	0.6	4.0	114
Mean ± SEM	37.1 ± 15.5	1.4 ± 0.2	145 ± 21	51 ± 20	1.4 ± 0.9	3.8 ± 0.1	99 ± 4
Normal range	*	< 1.2	< 80	< 30	< 1.0	3.5–5.5	70–110

* Males: 35–70 (18); Females: 27–63 (18).

TABLE IV
Plasma levels of amino acids lysine and methionine (nmol/ml)

Patient	Lysine	Methionine
1	133	32
2	165	28
3	151	27
6	123	37
8	120	29
11	152	35
12	155	34
13	144	33
14	135	35
Mean ± SEM	142 ± 5	32 ± 1.2
Controls	245 ± 12	34 ± 2

DISCUSSION

The results presented show a high prevalence of low plasma carnitine in patients on home TPN treatment for more than 1 year.

The reasons for the low plasma carnitine levels in these patients are not clear. Possible mechanisms include: decreased intake, impaired production, and increased wasting.

Exogenous carnitine is derived from the diet, mainly from meat, eggs, and dairy products and, to a lesser extent, from different vegetables and fruits. It is absorbed mainly through an active process in the proximal jejunum.[22] Our patients had little or no carnitine absorption because of the nature of their intestinal diseases, and severe malabsorption. Carnitine can be synthesized by humans and it has been suggested that 15 to 20 mg of the 40-mg daily requirement of carnitine are produced endogenously in the absence of carnitine intake.[4] Surgical patients receiving TPN were shown to develop a progressive decrease in plasma carnitine levels within 20 to 40 days,[6] indicating that in the postsurgical period endogenous carnitine production cannot maintain normal plasma levels.

Impaired carnitine synthesis is another possible mechanism. Lysine deficiency has been shown to lead to low plasma carnitine levels in rats.[23] Our patients had significantly low plasma lysine levels, raising the possibility of inadequate precursors for carnitine synthesis. Interestingly, the low plasma lysine occurred despite the high intake of lysine ranging between 3 to 5 gm/day. Lysine requirements in healthy adults have been estimated in various studies to be between 12 to 24 mg/kg/day.[24]

Impairment in the transsulfuration pathway, which is crucial for the production of *S*-adenosyl methionine, can reduce carnitine production.[16] It has been shown that the intravenous administration of methionine leads to lower cystine plasma levels,[25] as well as low carnitine[16] when compared to enteral intake, suggesting that utilization of intravenous methionine is less efficient than that administered orally.

Patients on prolonged TPN develop liver damage manifested histologically as steatosis, choleslasis and triaditis.[8–15] The mechanisms leading to this damage are not yet well understood. Because of the steatosis noted in both TPN-induced-liver damage and in primary carnitine deficiency the possibility has been raised that carnitine deficiency may play a role in the genesis of TPN liver disease. In our patients, a significant inverse correlation was found between the plasma carnitine and the alkaline phosphatase levels, which supports this hypothesis. The significant correlation between the serum albumin and the plasma creatinine could be interpreted as cause and effect, namely that liver dysfunction secondary to carnitine deficiency leads to de[illegible] albumin synthesis. It is also possible that synth[illegible] both carnitine and albumin is impaired because of the liver disease in these patients caused by factors other than carnitine. Recently Bowyer et al.[26] observed no improvement in patients' liver function tests after carnitine supplementation. However, the carnitine was administered for only one month. Two of the four patients were diabetic and insulin-dependent, and in a third patient the supplementation was interrupted because of sepsis.

It is evident that long-term TPN is associated with low plasma carnitine levels. The functional significance of this observation is not clear. Arbeit et al (unpublished data) reported a significant correlation between the plasma carnitine level and muscle carnitine content. Nevertheless, it is not certain that low plasma levels in our patients indicate deficiency of carnitine. Nor is it clear that acquired carnitine deficiency results in the same metabolic and clinical aberations as primary deficiency. The determination of the significance of the low plasma carnitine in home TPN patients and whether carnitine supplementation is necessary requires a placebo-controlled randomized study performed over a prolonged period.

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