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Carnitine Levels in Skeletal Muscle of Malnourished Patients Before and After Total Parenteral Nutrition

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ABSTRACT Carnitine is necessary for the transport of long-chain fatty acids across the mitochondrial membrane and it is derived from the diet and from endogenous synthesis from lysine and methionine. Of the body's carnitine pool, about 98% is located in skeletal muscle tissue. Skeletal muscle carnitine levels were determined in two groups of malnourished patients, eight patients with anorexia nervosa with a weight loss of 32.4% ± 1.8 (mean ± SEM) and six surgical patients with major gastrointestinal disorders and a weight loss of 15.2% ± 2.7. Their hepatic and kidney functions were normal. On admission, the muscle carnitine levels were 16.9 ± 4.0 μmol/g dry weight (mean ± SD) for the surgical patients and 20.8 ± 5.0 μmol/g dry weight for the anorexia nervosa patients, which corresponded to carnitine levels seen in healthy subjects. No statistical significance was found between the two groups. Total parenteral nutrition was given to the surgical patients for 2 weeks and to the anorexia nervosa patients for 3–5 weeks. No statistical difference in muscle carnitine levels was found in either group after nutritional support. These malnourished patients had no decreased muscle carnitine levels on admission and maintained them during several weeks of total parenteral nutrition.

INTRODUCTION

Carnitine is an essential co-factor in the transfer of long chain fatty acids across the inner mitochondrial membrane [1]. Furthermore, carnitine may also play a part in other metabolic processes, such as facilitation of branched-chain 2-oxo acid oxidation and as a reversible sink for acyl residues in the generation of CoASH [2]. In the synthetic pathway of carnitine, the precursor amino acids are lysine and methionine and the co-factors are iron, ascorbic acid and pyridoxine. The final reaction, hydroxylation of gamma-butyrobetaine, occurs in the liver and kidney in man. Thereafter carnitine is transported via plasma to, amongst other tissues, skeletal muscle. The body's supply of carnitine is derived partly from food and partly by endogenous synthesis. The relative contributions of endogenously synthesised and dietary carnitine in maintaining tissue stores in clinically normal and abnormal states have not been established.

In man, plasma carnitine levels have been observed to decline in protein-calorie malnutrition, malabsorption, Crohn's disease and anorexia nervosa [3, 4]. It has also been anticipated that carnitine deficiency may develop in patients on total parenteral nutrition since solutions given do not contain carnitine [5, 6]. Plasma carnitine is usually used to assess carnitine status due to its easy availability. Since about 98% of the total body carnitine is in muscle tissue [7], we thought it would be of interest to determine muscle carnitine levels in two groups of patients with malnutrition due to major gastrointestinal disorders and anorexia nervosa, before and after total parenteral nutrition.

PATIENTS MATERIALS AND METHODS

Patients

This study was conducted on two groups of malnourished patients: anorexia nervosa (AN) and surgical patients with major gastrointestinal disorders (GI). Eight female patients (mean age 17 years) with severe anorexia nervosa admitted to the paediatric department for nutritional therapy, were studied. Their weight loss was 32.4% ± 1.8 (mean ± SEM) of premorbid body weight. The other group comprised of six surgical patients (four males and two females) with a mean age of 60 years (range 30–82) and had a weight loss of 15.2% ± 2.7 (mean ± SEM) of premorbid body weight. According to biochemical and anthropometric measurements and skin test reactivity on admission, the surgical patients were considered malnourished based on criteria previously described [8]. Liver and kidney

functions determined by routine laboratory tests were normal in all patients.

Nutritional support

The AN patients received total parenteral nutrition (TPN) for 23–35 days (mean 31 days). The mean energy supply from TPN was 69 kcal/kg BW/day and the mean nitrogen supply was 0.38 g/kg BW/day. The AN patients were allowed to eat and drink freely during TPN. The GI patients received TPN for 14 days except for one who received TPN for 7 days. Their mean energy supply was 43 kcal/kg BW/day and their mean nitrogen supply was 0.20 g/kg BW/day. The non-protein calories were given as 1:1 glucose and fat (Intralipid®, Kabi Vitrum, Sweden), and the nitrogen as a balanced amino acid solution (Vamin®, Kabi Vitrum, Sweden). Energy and nitrogen supply were calculated from weight on admission. Electrolyte, trace element and vitamin supplements were added to the solutions.

Methods

Percutaneous muscle biopsies were taken before and after nutritional support from the lateral portion of the quadriceps femoris muscle as described by Bergström [9]. Carnitine was assayed as described in [10], giving the sum of free and acid-soluble carnitine esters. Analyses of adenosine-triphosphate, phosphocreatine, creatine and glycogen were performed as described by Harris and colleagues [11] and the sum of phosphocreatine and creatine was taken as the total creatine pool.

Statistics

The non-parametric Wilcoxon's two sample test, paired and not paired, were used for calculating the statistical significance of difference before and after nutritional support and between the groups. Spearman's rank sum test was used for calculation of correlations [12].

RESULTS

The body weight at admission for the AN patients was 36.3 ± 1.3 kg (mean ± SEM) and for the GI patients 64.4 ± 4.5 kg. During 3–5 weeks of TPN (AN patients) and 2 weeks of TPN (GI patients) the weight gain was 8.9 ± 1.4 kg (mean ± SEM) and 3.5 ± 0.7 kg, respectively.

The concentrations of carnitine in skeletal muscle tissue in the AN and GI patients on admission (Table 1) were within the range previously found in healthy subjects. 6.5–24.1 μmol/g dry weight, median value 17.9 [13]. There was no difference in the mean carnitine levels between the two groups before TPN, irrespective of whether the base of reference was dry weight or total creatine [14]; GI versus AN, 0.14 ± 0.01 mol carnitine per mol total creatine (mean ± SEM) versus 0.15 ± 0.01 mol carnitine per mol total creatine (Wilcoxon's two-sample test, not paired).

Table 1 Total acid soluble carnitine concentration in skeletal muscle before and after total parenteral nutrition

	Carnitine, μmol/g dry weight			
	GI		AN	
Patient No	Before	After	Before	After
1	16.4	18.0	21.4	20.2
2	17.5	14.6	21.1	17.0
3	22.2	17.4	22.6	24.2
4	19.7	18.8	18.9	21.2
5	14.5	16.6	15.9	14.8
6	10.8	14.8	19.1	13.5
7			15.6	16.1
8			31.6	15.7
Mean	16.9	16.7	20.8	17.8
SEM	1.6	0.7	1.8	1.3
Significance*	ns		ns	

* Wilcoxon's test for paired samples.

No significant change occurred in response to TPN, and there was still no difference in the mean carnitine levels between the two groups, irrespective of whether the base of reference was dry weight (Table 1) or total creatine; GI 0.14 ± 0.01 mol carnitine per mol total creatine (mean ± SEM) and AN 0.14 ± 0.01 mol carnitine per mol total creatine.

The two patient groups were pooled before calculation of any relationship of carnitine to other variables since no difference in mean carnitine levels was found between them. A statistically significant correlation was found between carnitine and ATP levels before nutritional support (Spearman's correlation coeff. $r_s = 0.5275$, ($p < 0.05$), but not after. No significant relationships were found between carnitine and phosphocreatine and glycogen, respectively. The mean values for ATP, phosphocreatine and glycogen before and after TPN are given in Table 2.

DISCUSSION

Rudman and colleagues [15] have estimated the daily endogenous production of carnitine to be about 100–125 μmol and the dietary intake to be about 400 μmol on

Table 2 ATP, phosphocreatine and glycogen in skeletal muscle before and after total parenteral nutrition (mean ± SEM)

Component per g dry weight	Before TPN $n = 14$	After TPN $n = 14$
ATP (μmol)	21.8 ± 1.0	22.3 ± 0.9
Phosphocreatine (μmol)	69.6 ± 4.2	69.3 ± 1.6
Glycogen (μmol glucosyl units)	334 ± 32	463 ± 38

an ordinary diet. It is therefore unlikely that healthy individuals develop carnitine deficiency. The weight loss in the malnourished patients in this study was great; mean value of 32.4% and 15.2% for the AN and GI patients, respectively. This implies that their diets before admission were insufficient in energy and probably also in protein and conceivably in some vitamins and trace elements. Despite this, the carnitine levels in muscle tissue were in the same range as those found in apparently healthy individuals [13]. Several factors may contribute to this finding, which this study does not allow us to differentiate between. The dietary carnitine may have been at least about 100 μmol per day (assuming all was absorbed), i.e., one quarter of the normal intake. The Swedish diet usually contains high amounts of animal protein and dairy products, which are food items with a high carnitine content. During muscle tissue breakdown, carnitine is released into plasma and excreted into urine [16, 17]. Some of the carnitine released into plasma may be reutilised.

Hahn and colleagues [18] reported that adult surgical patients were capable of maintaining plasma carnitine levels up to the 20th day of TPN. Over days 20–40 of TPN there was a gradual decline. Worthley and colleagues [19] described one patient on long-term TPN over 1 year, who possibly developed carnitine deficiency. He also had kidney and liver abnormalities. Later, the same authors described two patients with normal hepatic function who showed low plasma level and urinary excretion of carnitine after 34 and 39 months of TPN [20]. After carnitine administration, lethargy and weakness resolved in one patient and the other came into a positive carnitine balance. These findings were taken as an indication of an inadequate endogenous balance of carnitine for normal daily requirement in these patients.

It should be stressed, however, that plasma levels of total carnitine need not necessarily reflect the body stores of carnitine. In normal subjects, no correlation has been found between plasma and muscle tissue carnitine levels [13]. It is not known how well urinary carnitine excretion reflects body carnitine stores. In normal subjects put on a carnitine free diet the urinary excretion declined to about 100 μmol/day after 6 days [15] and it increased considerably after trauma [21, 17]. In our study, we have determined muscle carnitine levels, which must be the most valid indicator of the body carnitine pool. The AN patients received TPN for 23–35 days and the GI patients TPN for 14 days except one (7 days). The muscle carnitine levels remained unchanged, independently of the reference base used.

The most established function of carnitine is the transfer of long chain fatty acids across the inner mitochondrial membrane, but carnitine may be important in other cellular processes as well [2]. In this study we found a significant relationship between carnitine and ATP before nutritional support, which is in agreement with earlier findings in multiply injured patients [10].

In summary, it seems that patients with rather severe malnutrition and recent weight loss but with no serious disturbances in liver and kidney function are able to maintain carnitine levels in muscle tissue, which can be taken as an indirect estimate of their body carnitine stores. Furthermore, TPN without carnitine supplementation for 2 weeks (GI patients) or for 3–5 weeks (AN patients) did not influence the muscle carnitine levels.

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