0148-6071/81/0506-0505$02.00/0
JOURNAL OF PARENTERAL AND ENTERAL NUTRITION
Vol. 5, No. 6
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Urinary Carnitine Excretion in Surgical Patients on Total Parenteral Nutrition

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ABSTRACT. Urinary free and total carnitine excretions were measured in 41 normal adults and seven surgical patients on fat-free total parenteral nutrition for 8 to 45 days. The means (±SEM) of urinary free and total carnitine excretions in normal adults were 162 ± 19 and 328 ± 28 μmol/days, respectively. All of the patients exhibited protein-calorie malnutrition with a mean carnitine intake of 11.6 ± 1.5 μmol/day. Under this stringent carnitine economy with the adequate supply of lysine and methionine, urinary total carnitine excretion significantly reduced to 127 to 162 μmol/day. This probably reflects the carnitine biosynthetic rate. However, during the periods of operation and/or infection, urinary total carnitine excretion significantly increased 2- to 7-fold that of normal levels. Significant positive correlation was found between the two forms of urinary carnitine and total nitrogen excretions. Serum free and total carnitine levels in patients were significantly higher than normal adults. Such findings can be explained by the endocrine responses to the stress phenomenon and indicate a catabolic response of skeletal muscle in which most of the body carnitine resides. This can impair their carnitine status.

It is now established that carnitine in the body is derived from the intake of preformed exogenous carnitine[1] and synthesized from lysine and methionine.[2] Since carnitine has not been added to any commercially available parenteral fluids[3] it would be anticipated that carnitine deficiency may exist in patients on total parenteral nutrition (TPN). Indeed, we have reported inadequate carnitine status in these patients.[4]

MATERIALS AND METHODS

This study was conducted on two groups: normal adults and surgical patients. Normal adults were healthy Bangkok residents (28 males and 25 females) with a mean age of 35.6 ± 1.7 (±SEM). Seven patients were admitted at Ramathibodi Hospital. Their clinical data before receiving TPN are shown in Table I. Percutaneous subclavian vein catheterization was employed to deliver the fat-free TPN.[5] Their energy, glucose, total amino acid (AA), lysine, and methionine intakes were recorded. Patients #1, #3, #4, and #6 underwent the operation listed in Table I during the administration of TPN. The period of TPN lasted from 8 to 45 days. Patient #2 received TPN for two separate periods. The study was conducted in accordance with the principles for human experimentation as defined in the Declaration of Helsinki.

Venous blood was obtained from the normal adults after a 12- to 14-hr fast, and from each patient weekly between 7 to 8 AM during the study. Twenty-four hr urine samples were collected from normal adults 1 day prior to the venipuncture, using toluene as preservative. For patients, the samples were collected daily during the administration of TPN. The carnitine contents in serum, urine, and TPN solutions were determined by the enzymatic-radioisotopic method of McGarry and Foster.[6] Each sample was analyzed for both free and total carnitine contents. The acylcarnitine concentration was obtained from the difference between the total and free carnitine values. Carnitine excretion from the gastrointestinal tract was not measured. Urinary total nitrogen excretion was determined in patients during the administration of TPN.[7] Details of their nitrogen balance will be reported elsewhere. The protein calorie status in patients before the administration of TPN was assessed by the body mass index (BMI),[8] serum total protein, and albumin levels,[9] and creatinine-height index (CHI).[9, 10]

The Student t-test (one-tailed) and linear regression analysis were used to establish statistical significance.[11] Serum and urinary carnitine values (mean ± 1 SD) obtained from the normal adults were used to define the normal range.

RESULTS

The mean daily intake of energy, glucose, total amino acids, lysine, and methionine in each patient on TPN is listed in Table II. Their BMI, CHI, serum total protein, and albumin levels are tabulated in Table III. Carnitine was detected in FreAmine II (McGaw Lab, Irvine, CA) and Sohamin G (Tanabe Seiyaku Co, Osaka, Japan), which were the two types of crystalline AA solutions used in this study. Each 1000 ml of FreAmine and Sohamin G contained 7.1 and 26.7 μmol total carnitine, respectively. The total carnitine intake determined from the carnitine concentration of the AA solutions and the

Received for publication, October 16, 1980.
Accepted for publication, July 31, 1981.
This work was presented in part at the 2nd European Congress on Parenteral and Enteral Nutrition, Newcastle upon Tyne, England, September 7–10, 1980.
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TABLE I
Clinical data in patients on TPN

Patient	Age	Sex	Diagnosis	Operation
	yr			
1	15	F	Ileostomy postrupture of appendicitis	Closure of ileostomy
2	19	M	Colonocutaneous fistulae postrupture of appendicitis	None
3	21	M	Blunt traumatic duodenal rupture	1st: gastrojejunostomy 2nd: drainage of subhepatic abscess
4	22	M	Chemical stricture of esophagus	Esophagectomy with colon interposition
5	35	M	Rupture of empyema of gallbladder	None
6	50	M	Pyeloduodenal fistula	Ureterostomy
7	72	M	Postcholecystectomy	None

TABLE II
Intake in patients on fat-free TPN

Patient	Days on TPN	Mean intake/day			Mean lysine intake		Mean methionine intake	
		Energy	Glucose	Total AA				
		kcal		*g*	*g/day*	*mg/kg/day*	*g/day*	*mg/kg/day*
1	13	2104	485	42.55	2.96	118	2.25	90
2								
2.1	31	3362	774	54.12	9.26	234	4.08	103
2.2	13	3124	728	52.73	9.03	208	3.98	92
3	45	3019	707	48.11	8.03	182	3.63	82
4	18	1865	424	42.11	3.84	107	1.41	39
5	8	2344	551	35.18	7.53	140	3.32	62
6	23	2988	707	40.32	6.90	129	3.04	57
7	21	2322	535	45.28	7.75	114	3.41	50
Mean ± SEM		2642 ± 193	614 ± 46	45.05 ± 2.26	6.91 ± 0.82	154 ± 17	3.14 ± 0.32	72 ± 8

TABLE III
Protein-calorie status of patients before TPN

Patient	Height	Body weight	BMI	CHI	Serum protein	
					Total	Albumin
	m	*kg*	*kg/m²*		*g/dl*	
1	1.48	25.0	11.3	0.41	8.5	2.6
2	1.76	39.6	12.8	0.36	6.6	2.8
3	1.75	44.0	14.4	0.42	4.1	1.8
4	1.67	36.0	12.9	0.40	5.4	3.0
5	1.63	53.7	20.2	0.28	8.0	2.6
6	1.70	53.5	18.5	0.65	4.7	1.8
7	1.60	68.0	26.6	0.30	6.0	2.7

TABLE IV
Total carnitine intake and its urinary carnitine excretion in patients on TPN

Patient	Mean total carnitine intake		Mean urinary total carnitine	
	μmol/day	*μmol/kg/day*	*μmol/day*	*μmol/kg/day*
1	3.53	0.13	290	10.86
2				
2.1	16.03	0.38	162	3.79
2.2	15.62	0.36	127	2.65
3	14.13	0.35	1080	20.58
4	5.42	0.14	933	22.68
5	13.02	0.24	2337	43.52
6	11.94	0.22	2362	44.16
7	13.39	0.21	799	11.84
Mean ± SEM	11.64 ± 1.55	0.25 ± 0.10	1011 ± 318	20.01 ± 5.76

volume infused and urinary total carnitine excretion are listed for the seven individual patient in Table IV. The urinary-free acyl and total carnitine excretions in the normal controls and the individual TPN patient are tabulated in Table V. In two study periods, patient #2 had significantly lower urinary-free, acyl, and total carnitine excretions than normal adults. Opposite results were observed for patients #3, #4, #5, #6, and #7, whose clinical manifestations and laboratory investigations indicated bacterial infection during the administration of TPN. However, this was not related to subclavian vein catheterization. No significant difference was observed between patient #1 and normal adults.

Figure 1 shows the daily urinary-free, acyl, and total carnitine excretions in patients #1, #3, #4, and #6 who underwent surgery while receiving TPN. These four patients had increased urinary carnitine excretion above the preoperative levels on the day of operation and for several days following operation. Then their urinary carnitine excretion declined to the preoperative levels if there was no episode of postoperative infection. The second rise in urinary carnitine excretion in patients #3, #4, and #6 occurred concurrently with the bacterial infection. Patient #3 had the second peak of urinary carnitine excretion prior to the second operation, which declined after the surgical drainage of subhepatic pus collection. Patients #4 and #6 developed pneumococcal pneumonia and pseudomonas septicemia, respectively. A statistically significant relationship existed between urinary carnitine excretion and body temperature (Table VI). Urinary carnitine also correlated significantly with the total nitrogen excretion (Table VII). The mean (±SEM) serum-free, acyl, and total carnitine concentration in the TPN patients is compared with that in the normal controls (Table VIII).

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TABLE V
Urinary carnitine excretion in normal adults and surgical patients

Subject		Urinary carnitine, μmol/day[a]		
Group	No[b]	Free	Acyl	Total
Normal	41	162 ± 19	165 ± 13	328 ± 28
Patient				
1	13	135 ± 46	154 ± 76	290 ± 121
2				
2.1	31	50 ± 5[c]	112 ± 8[c]	162 ± 10[c]
2.2	13	44 ± 7[c]	83 ± 16[d]	127 ± 20[c]
3	45	679 ± 75[c]	402 ± 25[c]	1080 ± 89[c]
4	18	518 ± 62[c]	415 ± 70[d]	933 ± 116[c]
5	8	1524 ± 113[c]	813 ± 115[e]	2337 ± 208[c]
6	23	1948 ± 319[c]	415 ± 72[d]	2362 ± 345[c]
7	21	530 ± 76[c]	269 ± 43[f]	799 ± 116[c]

[a] Mean ± SEM.
[b] Number of normal subjects and number of days carnitine determined for the TPN patients.
[c] Significant difference from normal adults: $p < 0.0005$.
[d] Significant difference from normal adults: $p < 0.0025$.
[e] Significant difference from normal adults: $p < 0.005$.
[f] Significant difference from normal adults: $p < 0.025$.

DISCUSSION

All of the patients receiving TPN exhibited protein-calorie malnutrition (PCM) as evidenced by a CHI of less than 0.9 and serum albumin levels of less than 3.5 g/dl.[9] These indicate depleted lean body mass[9, 10, 12] and visceral protein status.[9] Only four out of seven patients had serum total protein of less than 6.5 g/dl. This is consistent with other reports that the serum total protein concentration is a less sensitive and specific index of the protein nutritional status.[9] All of the patients gave a history of weight loss, with five of them having a BMI of less than 20 kg/m^2.

Serum and urinary carnitine are regulated by both nutritional and endocrine factors. Decreased serum carnitine concentration and urinary carnitine excretion have been reported in subjects with protein-calorie malnutrition[13-17] and hypothyroidism.[18] The administration of adrenocorticotrophic hormone in the presence of intact adrenocortical and thyroid functions increases the serum

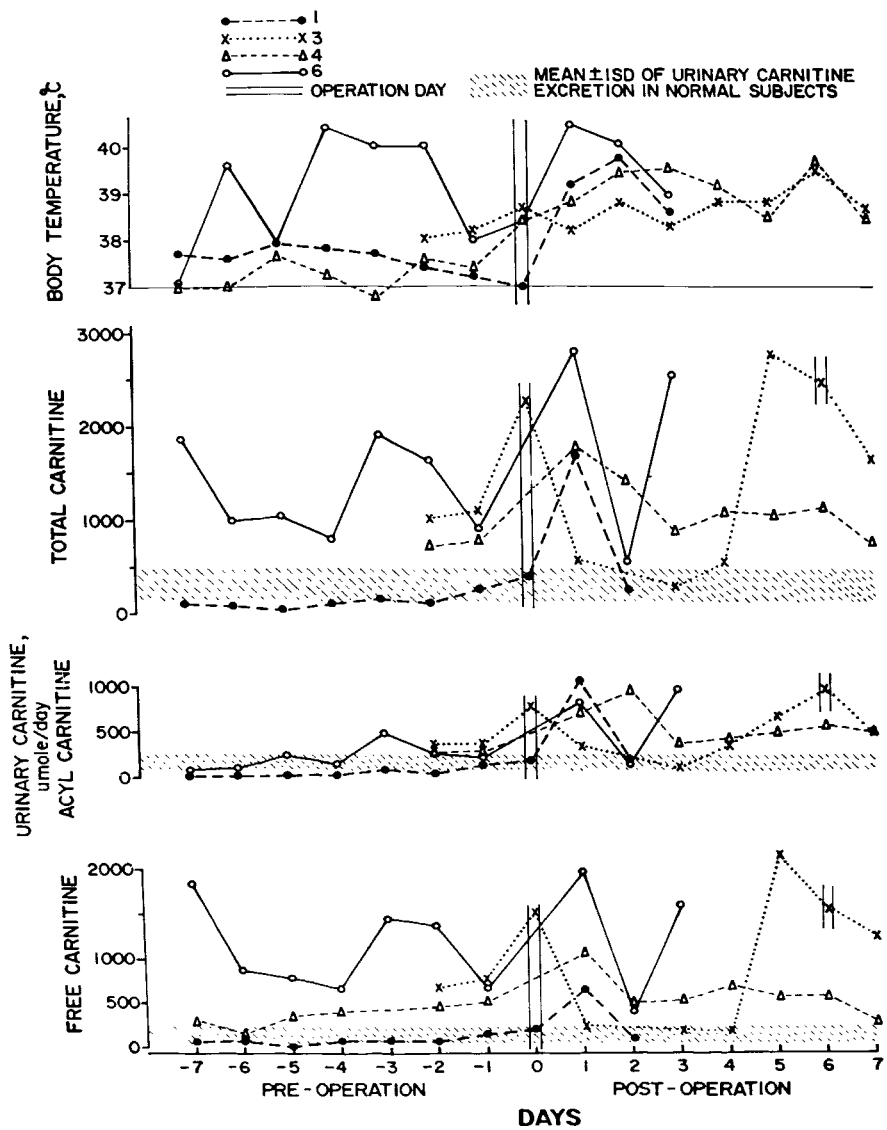

FIG. 1. The influence of body temperature and operation on urinary carnitine excretion in four patients.

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TABLE VI
Relationship between urinary carnitine excretion and body temperature in surgical patients

c = urinary carnitine (μmol/day)	t = a + bc (body temperature °C)	Correlation coefficient	DF	t Statistic	p
Free carnitine	37.56 + 0.0004c	0.3120	153	4.0487	<0.0005
Acyl carnitine	37.33 + 0.0015c	0.3930	153	5.2695	<0.0005
Total carnitine	37.46 + 0.0004c	0.3627	153	4.7981	<0.0005

TABLE VII
Relationship between urinary carnitine and total nitrogen excretion in surgical patients

c = urinary carnitine (μmol/day)	N = a + bc (total nitrogen, g/day)	Correlation coefficient	DF	t Statistic	p
Free carnitine	6.16 + 0.0026c	0.5648	146	8.2426	<0.0005
Acyl carnitine	5.52 + 0.0075c	0.5155	146	7.2442	<0.0005
Total carnitine	5.66 + 0.0023c	0.6080	146	9.2225	<0.0005

TABLE VIII
Serum carnitine levels in normal adults and surgical patients

Subject		Serum carnitine, μmol/l[a]		
Group	No	Free	Acyl	Total
Normal	53	64.7 ± 1.6	53.2 ± 3.8	117.9 ± 4.4
Patients on TPN				
0 wk	8	78.6 ± 14.1[b]	73.8 ± 14.0	152.6 ± 12.2[c]
1 wk	6	95.4 ± 25.2[d]	89.9 ± 22.0[d]	185.3 ± 43.7[e]
2 wk	7	86.6 ± 9.8[d]	59.5 ± 7.7	146.2 ± 10.4[b]
3 wk	5	83.5 ± 12.0[f]	59.7 ± 7.6	143.2 ± 12.7[g]

[a] Mean ± SEM.
[b] Significant difference from normal adults: $p < 0.025$.
[c] Significant difference from normal adults: $p < 0.005$.
[d] Significant difference from normal adults: $p < 0.0025$.
[e] Significant difference from normal adults: $p < 0.0005$.
[f] Significant difference from normal adults: $p < 0.0125$.
[g] Significant difference from normal adults: $p < 0.05$.

carnitine level and urinary carnitine excretion.[19, 20] Since our patients were malnourished, with a limited carnitine intake (Table IV), as they were receiving TPN, one would have expected a decreased urinary carnitine excretion. This was observed in patient #2 who was not septic and did not undergo surgery. He had significantly lower urinary-free, acyl, and total carnitine excretions than the normal adults (Table V). Patient #1 had low urinary carnitine excretion also during the study, except for the first 2 days after the operation (Fig. 1). This explains her mean urinary-free, acyl, and total carnitine excretions falling within the normal levels (Table V). Infection and tissue injury stimulated the adrenocortical release of cortisol.[21] The significant increase in the three forms of urinary carnitine excretion in patients #3 to #7 (Table V and Fig. 1) could be explained on this basis. This is supported by the significant positive correlation found between urinary carnitine excretion and body temperature (Table VI and Fig. 1). Our results agree with the report of Cederblad et al[22] who demonstrated a marked increase in urinary carnitine excretion in burned patients.

Rudman et al[15] reported that normal adults, with a carnitine intake of 380 to 450 μmol/day, excreted similar amounts of total carnitine in urine. However, when they were fed an oral diet with less than 10 μmol carnitine, but containing 2200 to 2400 kcal, 80 to 90 g protein with 3200 to 3400 mg lysine and 2000 to 2200 mg methionine, their urinary total carnitine excretion was 100 μmol/day. Similar findings were observed in patient #2. While receiving daily 16 μmoles carnitine, 3124 to 3362 kcal, 52.7 to 54.1 g AA containing 9030 to 9260 mg lysine, and 3980 to 4080 mg methionine, he excreted 127 to 162 μmol total carnitine (Tables II and IV). This probably reflects the carnitine synthesis. Since skeletal muscle is the major storage site of carnitine,[23–25] the increase in urinary carnitine excretion in patients #3 to #7, despite limited carnitine intake, may indicate a catabolic response of this tissue. This is supported by (1) the significant positive correlations found between the urinary carnitine and total nitrogen excretion (Table VII) and (2) the significant increase in serum-free and total carnitine levels (Table VIII). The 2- to 7-fold increases in urinary carnitine excretion in these patients could deplete their skeletal muscle carnitine content. It should be noted that Border et al[26] reported decreased skeletal muscle carnitine levels in septicemic patients without starvation. However, urinary carnitine excretion was not determined in their study.

The relationship between carnitine and energy metabolism is well recognized. Carnitine participates in shuttling long-chain acyl residues across the inner membrane of mitochondria.[27] It is therefore important for fatty acid oxidation. Besides, carnitine may indirectly participate in regulating the rate of glycolysis, by increasing the activity of pyruvate dehydrogenase.[28] The biological significance of carnitine in man was demonstrated by two forms of hereditary carnitine deficiencies: myopathic and systemic.[29] Patients receiving intravenous fat emulsion have been reported to experience significant decreases in serum carnitine[30, 31] and urinary carnitine levels.[30] Though our TPN formula is a fat-free regimen, the 2- to 7-fold increases in urinary carnitine excretion in the presence of limited carnitine intake in some patients receiving TPN (Table IV) may be indicative of carnitine deficiency. The effects of such acquired carnitine deficiency are now under investigation.

ACKNOWLEDGMENTS

This work was supported by a grant from the Faculty of Medicine, Ramathibodi Hospital, and Otsuka Pharmaceutical Factory, Inc.

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