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Effects of L-Carnitine Supplemented Total Parenteral Nutrition on Lipid and Energy Metabolism in Postoperative Stress

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ABSTRACT. During episodes of trauma carnitine-free total parenteral nutrition (TPN) may result in a reduction of the total body carnitine pool, leading to a diminished rate of fat oxidation. Sixteen patients undergoing esophagectomy were divided randomly in two equal isonitrogenous groups (0.2 g/kg·day). Both received TPN (35 kcal/kg·day; equally provided as long-chain triglycerides and glucose) over 11 days without (group A) and with (group B) L-carnitine supplementation (12 mg/kg·day = 75 μmol/kg·day). Compared with healthy controls, the total body carnitine pool prior to the operation was significantly reduced in both groups, suggesting a state of semistarvation and muscle wasting. In group A the plasma levels of total carnitine and its subfractions (free carnitine, short- and long-chain acylcarnitine) remained stable during the study whereas in group B the total plasma carnitine concentration rose mainly due to an increase in free carnitine. In group A the cumulative urinary carnitine losses were 11.5 ± 2.6 mmol (=15.5 ± 3.1% of the estimated total body carnitine pool). In group B 3.1 ± 1.9 mmol (=11.1 ± 7.6%) of the infused carnitine was retained in the immediate postoperative phase until day 6, but this amount was completely lost at completion of the study period.

No significant differences in the respiratory quotient or in the plasma levels of triglycerides, free fatty acids, and ketone bodies were observed, between or within the groups, before the operation and after 11 days of treatment.

It is concluded that the usefulness of carnitine supplementation during postoperative TPN was not apparent in the present patient material. (*Journal of Parenteral and Enteral Nutrition* **12**:555–562, 1988)

L-carnitine is required for the transport of long-chain free fatty acids into mitochondrias thereby facilitating β-oxidation.[1] Generally, the total body pool of carnitine is balanced by dietary intake, endogenous biosynthesis in liver and kidneys, and by urinary excretion.[2-4] Usually no exogenous carnitine is provided in stressed patients on total parenteral nutrition (TPN) although their urinary carnitine excretion is known to be markedly higher than normal.[5,6] Moreover, since stress is associated with enhanced lipolysis, it is reasonable to expect an increased demand for carnitine, especially considering the high supply of long-chain triglycerides during TPN. Thus, such a patient may develop carnitine deficiency resulting in a diminished rate of fat oxidation.[8] Consequently, amino acids could be partially consumed as fuel in the gluconeogenetic system, thereby leading to a deterioration of the nitrogen balance.[8,9]

MATERIALS AND METHODS

Subjects

Sixteen surgical patients with epidermoid carcinoma undergoing total esophagectomy were divided randomly in two groups of eight to receive exclusive TPN without (group A) and with (group B) L-carnitine supplementation during the first 11 postoperative days (Table I).

Exclusion criteria were septicemia, liver cirrhosis with ascites and renal failure, as well as abnormal lipid and endocrinological status. The patients were informed about the nature of the investigation before participating in the study and their consent was obtained. The procedures followed were in accord with the Helsiniki Declaration from 1975.

A sex-matched control group of 24 healthy subjects was examined as reference for carnitine measurements in plasma and urine. Normal muscle carnitine levels were adopted from Rössle et al. [11] All other clinical biochemistry reference values are derived from the clinical laboratory in Lausanne.

Experimental Procedure

On the day before the operation (day −1) a venous blood sample was obtained and indirect calorimetry was performed. Additionally, 24-hr urine was collected. Operations, which were performed by the same surgeon, included a thoracotomy followed by a laparotomy under general anesthesia (5.4 ± 1.4 hr). Selected biopsies from musculus rectus abdominis were taken at the beginning of the operation from 10 patients (group A: n = 4; group B: n = 6). Postoperatively, all patients were admitted to the Intensive Care Unit for mechanical ventilation for at least 2 days (3.3 ± 1.2 days).

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TABLE I
Sex, age, and physical characteristics of the controls and of the patients treated with TPN without (group A) and with (group B) carnitine supplementation (Mean ± SEM)

	Controls (n = 24)	Group A (n = 8)	Group B (n = 8)
Sex	12 F/12 M	3 F/5 M	2 F/6 M
Age (years)	27.0 ± 0.9	62.7 ± 15.5	65.8 ± 8.6
Weight (kg)	58.5 ± 2.0		
Preoperative (day −1)		64.1 ± 2.8	64.2 ± 4.3
Postoperative (day 11)		63.4 ± 2.9	63.3 ± 4.3
Height (m)	1.66 ± 0.02	1.67 ± 0.04	1.70 ± 0.03
Body surface area* (m^2)	1.65 ± 0.03	1.72 ± 0.05	1.74 ± 0.06
Body mass index† (kg/m^2)	21.2 ± 1.8	22.8 ± 1.1	22.2 ± 1.4

* Calculated according to Dubois and Dubois.[10]
† Ratio weight/(height)^2.

TABLE II
Energy and protein intake over the 11 postoperative days in the patients treated with TPN without (group A) and with (group B) carnitine supplementation (Mean ± SEM)

	Group A (n = 8)	Group B (n = 8)
Energy* (kcal/kg·day)	34.7 ± 0.7	32.4 ± 1.3
Nitrogen† (g/kg·day)	0.20 ± 0.01	0.19 ± 0.01
L-carnitine‡ (g/kg·day)		11.9 ± 0.4

* Equally provided by fat and glucose (Lipovenös and Glucosteril 40%, Fresenius AG, Bad Homburg, FRG).
† Proteinsteril (Fresenius AG, Bad Homburg, FRG).
‡ Kindly provided by Fresenius AG, Bad Homburg, FRG.

Continuous TPN was started on the first postoperative day (day 1), by steadily increasing the infusion rate until day 3. The full regimen provided 35 kcal/kg·day of total energy (nonprotein energy was supplied equally as long-chain triglycerides and glucose) and 0.2 g of nitrogen/kg·day. Electrolytes, trace elements, and vitamines were given as requested.[12] The nutrients were mixed in 3-liter nutritional bags and infused continuously via a central venous catheter. Patients in group B were given supplements of 2126 μmol L-carnitine/1000 kcal (=12 mg/kg·day or 75 μmol/kg·day). The actual nutrient intake was controlled by weighing the nutritional bags before and after infusion. On the 11th postoperative day indirect calorimetry was repeated. Postoperative blood and urine samples were obtained 1 day after operation (day 1) and then every other day (days 3, 5, 7, 9, and 11) without modifying the TPN infusion rate (Table II).

Carnitine

The heparinized blood was immediately centrifuged and deproteinized. The muscle biopsies were instantly frozen in liquid nitrogen and subsequently lyophilized. Prior to the carnitine assay all visible blood and connective tissue were carefully removed.

As urinary carnitine is closely related to the dietary carnitine intake[13], 24-hr urine was collected during 5 consecutive days in healthy controls in order to get a carnitine excretion representative for their nutritional habits. The average individual carnitine output was used to calculate the mean carnitine excretion of the control group.

All plasma, urine, and muscle samples were stored at −70°C until analyzed. Plasma, urine, and muscle-free carnitine (FC), total acid-soluble carnitine (TASC), and long-chain acylcarnitine (LCC) were measured using a radiochemical-enzymatic assay according to Rössle et al.[14] Short-chain acylcarnitine (SCC) was calculated as the difference of TASC and FC. Total carnitine (TC) was obtained by addition of FC, SCC, and LCC. The ratio of acylcarnitines (AC) to FC was calculated using the formula:

$$AC/FC = (SCC + LCC)/FC$$

Plasma concentrations are given in μmol/liter, urinary outputs are expressed as μmol/24 hr and muscle concentrations are referred to noncollagen protein (μmol/g NCP) which was determined according to Lowry et al.[15] On days 2, 4, 6, 8, and 10 urine was not collected. For calculation of the cumulative urinary losses, the carnitine excretions were estimated based on the outputs before and after these days.

As muscle tissue is known to be almost identical with the total body carnitine pool,[16] the preoperative carnitine reserves in our patients were estimated from the total carnitine concentration in the lyophilized biopsy and by considering the muscle mass. For this estimation it was assumed that muscle dry weight in humans corresponds to 23.8% of the muscle wet weight.[17] The muscle mass was obtained by using the creatinine excretion, assuming that 1 g of creatinine excretion/24 hr is equivalent to 20 kg of skeletal muscle tissue.[18]

Indirect Calorimetry

An indirect calorimeter with a transparent hood, built in Lausanne and described by Jéquier[19] was used. The energy expenditure (EE), respiratory quotient (RQ), and nonprotein respiratory quotient (np-RQ) were calculated from calorimetric values and urinary nitrogen excretion.[19] The accuracy of the method has been shown to be within 1%. Heart rate and axillary temperature were continuously recorded during the calorimetric measurements lasting 1 hr.

Laboratory

Plasma-free fatty acids (FFA) were determined according to Heindel et al,[20] β-hydroxybutyrate and acetoacetate to Mellanby et al[21] and triglycerides (TG) to Stavropoulos and Crouch.[22] Total nitrogen in 24-hr urine collections were measured by chemiluminescence[23] (Antek Auto-Analyzer 703 C). Plasma insulin was determined by radioimmunoassay according to Herbert et al[24] and glucagon by radioimmunoassay (antiserum RCS 5).

Statistics

All the results are expressed as mean ± standard error of the mean (SEM). Statistical differences were assessed using nonparametric tests according to Mann-Whitney or Wilcoxon for unpaired or paired comparisons of the patients, respectively. For simultaneous comparison of both patient groups with the control group, one-sided ANOVA was used.[25]

RESULTS

Plasma Carnitine

Compared with the control group, a trend towards higher preoperative concentrations of FC and TC is noted, accompanied by a significantly lowered AC/FC ratio in both groups. The concentrations of TC and its subfractions, as well as the AC/FC ratio, are similar between the two groups of patients.

Without supplementary carnitine, no essential changes in plasma concentrations of TC and its subfractions are observed, although a temporary decrease reaching its minimum on day 5 is noted (Table III). Carnitine supply is associated with a steady postoperative increase of FC and TC while the concentrations of acylcarnitines (SCC and LCC) show only minor changes. Thus, the AC/FC ratio declines to a minimum value on the 7th postoperative day and is significantly lower than the initial ratio prior to the operation.

Urinary Carnitine

As with the results for plasma, in comparison with the control group, patients in both groups show slightly higher preoperative FC and TASC outputs together with a markedly lower AC/FC ratio (Table IV). The excretion of FC, TASC, and SCC however is similar in both groups prior to the operation.

TABLE III

Plasma carnitine concentrations (μmol/liter) before and after elective surgery in patients treated with TPN without (group A) and with (group B) carnitine supplementation (Mean ± SEM)

	Carnitine				Ratio acyl-/free (AC/FC)
	Free (FC)	Short-chain (SCC)	Long-chain (LCC)	Total (TC)	
Controls (n = 24)	36.9 ± 2.2	8.8 ± 0.7	3.6 ± 0.3	49.2 ± 2.8	0.35 ± 0.02
Group A (n = 8)					
Day −1	44.9 ± 4.4	8.1 ± 1.2	2.7 ± 0.6	55.6 ± 4.8	0.23 ± 0.05*
Day 1	44.2 ± 3.4	6.3 ± 1.1	2.3 ± 0.5	52.7 ± 4.8	0.19 ± 0.02*
Day 3	38.0 ± 4.4	5.8 ± 1.0	2.7 ± 0.8	46.5 ± 5.9	0.22 ± 0.02*
Day 5	36.8 ± 4.7	5.3 ± 0.8	2.5 ± 0.5	44.5 ± 5.6	0.21 ± 0.02*
Day 7	38.0 ± 5.1	6.3 ± 1.1	3.0 ± 0.9	47.3 ± 6.3	0.23 ± 0.02*
Day 9	43.1 ± 6.4	5.7 ± 1.0	3.0 ± 0.6	51.8 ± 7.6	0.20 ± 0.02*
Day 11	45.5 ± 6.3	5.7 ± 0.9	3.0 ± 1.0	54.2 ± 7.3	0.16 ± 0.02*†
Group B (n = 8)					
Day −1	47.7 ± 3.8	7.8 ± 1.5	2.8 ± 0.3	58.3 ± 4.3	0.23 ± 0.04*
Day 1	42.0 ± 3.0	7.5 ± 1.9	1.8 ± 0.1*	51.3 ± 3.5	0.23 ± 0.05*
Day 3	59.0 ± 10.5*	7.0 ± 1.8	2.3 ± 0.4*	68.2 ± 12.2*	0.16 ± 0.02*
Day 5	70.5 ± 7.9*‡	7.9 ± 1.7	3.1 ± 0.4	81.5 ± 9.3*‡	0.16 ± 0.02*
Day 7	81.6 ± 8.0*†‡	7.0 ± 1.5	3.2 ± 0.4	91.8 ± 9.4*†‡	0.12 ± 0.02*†‡
Day 9	82.9 ± 11.2*†‡	8.8 ± 1.8	2.9 ± 0.5	94.6 ± 13.0*†‡	0.14 ± 0.02*‡
Day 11	84.5 ± 6.8*†‡	11.0 ± 2.9	3.3 ± 0.3	98.8 ± 9.3*†‡	0.16 ± 0.03*

* $p \leq 0.05$ significant *vs* controls.
† $p \leq 0.05$ significant *vs* day −1 same group.
‡ $p \leq 0.05$ significant *vs* same day group A.

TABLE IV

Urinary carnitine excretion (μmol/24 hr) before and after elective surgery in patients treated with TPN without (group A) and with (group B) carnitine supplementation (Mean ± SEM)

	Carnitine			Ratio acyl-/free (AC/FC)
	Free (FC)	Short-chain (SCC)	Total (TC)	
Controls (n = 24)	180 ± 23	225 ± 27	405 ± 48	1.77 ± 0.18
Group A (n = 8)				
Day −1	299 ± 93	195 ± 37	494 ± 100	1.19 ± 0.56*
Day 1	794 ± 94*†	379 ± 92*†	1173 ± 186*†	0.49 ± 0.05*†
Day 3	732 ± 297*	278 ± 81	1010 ± 372*	0.63 ± 0.21*
Day 5	536 ± 186*	313 ± 68	849 ± 251*	0.70 ± 0.16*
Day 7	536 ± 122*	390 ± 108	926 ± 220*	0.75 ± 0.10*
Day 9	448 ± 138*	248 ± 72	696 ± 230*	0.59 ± 0.09*
Day 11	426 ± 95*	286 ± 56	712 ± 137*	0.77 ± 0.17*
Group B (n = 8)				
Day −1	232 ± 71	209 ± 60	441 ± 106	1.04 ± 0.18*
Day 1	1021 ± 275*†	320 ± 106	1341 ± 356*†	0.71 ± 0.40*
Day 3	3063 ± 415*†‡	583 ± 77*†‡	3646 ± 450*†‡	0.22 ± 0.04*†‡
Day 5	3565 ± 373*†‡	656 ± 82*†‡	4221 ± 429*†‡	0.19 ± 0.02*†‡
Day 7	5131 ± 710*†‡	819 ± 49*†‡	5951 ± 716*†‡	0.19 ± 0.02*†‡
Day 9	4522 ± 626*†‡	893 ± 126*†‡	5415 ± 734*†‡	0.20 ± 0.02*†‡
Day 11	4900 ± 727*†‡	980 ± 115*†‡	5880 ± 826*†‡	0.21 ± 0.02*†‡

* $p \leq 0.05$ significant *vs* controls.
† $p \leq 0.05$ significant *vs* day −1 same group.
‡ $p \leq 0.05$ significant *vs* same day group A.

Irrespective of carnitine supply, the immediate response to trauma is reflected in a 2- to 3-fold increase of FC and TASC output in both patient groups 1 day after surgery. Without supplementary carnitine this response remains operative throughout the study; on the last day of the study period excretion is still about 40% higher than the preoperative level. In the supplemented group, a continuous postoperative increase in the excretion of FC and TASC is observed until day 7. As the elevation of FC output is more pronounced than that of SCC, the resulting AC/FC ratio is significantly reduced on and after day 3.

Plasma and Urinary Correlations

Significant positive correlations between plasma and urinary levels of FC ($r = 0.907; p \leq 0.01$), TC and TASC ($r = 0.898; p \leq 0.01$), and between the plasma and the urinary AC/FC ratio ($r = 0.824; p \leq 0.01$) are observed in patients receiving supplementary carnitine.

Muscle Carnitine

The combined muscular concentrations of FC and TC in patients of groups A and B are lower than in healthy volunteers, whereas the SCC levels are similar to those found in controls (Table V). In contrast with plasma and urine, the patients consequently exhibit a higher AC/FC ratio in muscle compared with healthy subjects.

The estimated normal total body carnitine pool amounts to 131 ± 6 mmol. Compared with this figure, the patients in both groups show a considerably diminished total carnitine pool of 75 ± 8 mmol, both groups being equally affected (75 ± 11 and 74 ± 13 mmol).

Cumulative Carnitine Balance

As the patients in group A received no exogenous carnitine, the carnitine balance is continuously negative during the whole postoperative period (Fig. 1). The cumulative urinary losses until day 11 amount to 11.5 ±

TABLE V

Muscle carnitine concentrations and the estimated total body carnitine pool in patients with esophagus carcinoma and in healthy controls (Mean ± SEM)

	Carnitine				Ratio acyl-/free (AC/FC)
	Free (FC)	Short-chain (SCC)	Long-chain (LCC)	Total (TC)	
Controls (n = 15)					
Muscle biopsy (μmol/g NCP)*	25.2 ± 0.9	3.4 ± 0.5	0.25 ± 0.01	28.9 ± 1.0	0.15 ± 0.02
Pool† (mmol)	114.8 ± 6.0	15.0 ± 2.1	1.15 ± 0.08	130.9 ± 6.3	0.15 ± 0.02
Patients (n = 10)					
Muscle biopsy (μmol/g NCP)*	21.1 ± 2.3	3.7 ± 0.5	0.20 ± 0.02‡	25.0 ± 2.2	0.23 ± 0.05‡
Pool§ (mmol)	63.3 ± 8.3§	11.4 ± 1.9	0.59 ± 0.07§	75.3 ± 8.5§	0.23 ± 0.05‡

* NCP, noncollagen protein.

† Estimated by: (μmol/g muscle wet weight) · muscle mass; muscle mass: 1 g of creatinine excretion/24 hr = 20 kg muscle.[18]

‡ $p \leq 0.05$ significant *vs* controls.

§ $p \leq 0.01$ significant *vs* controls.

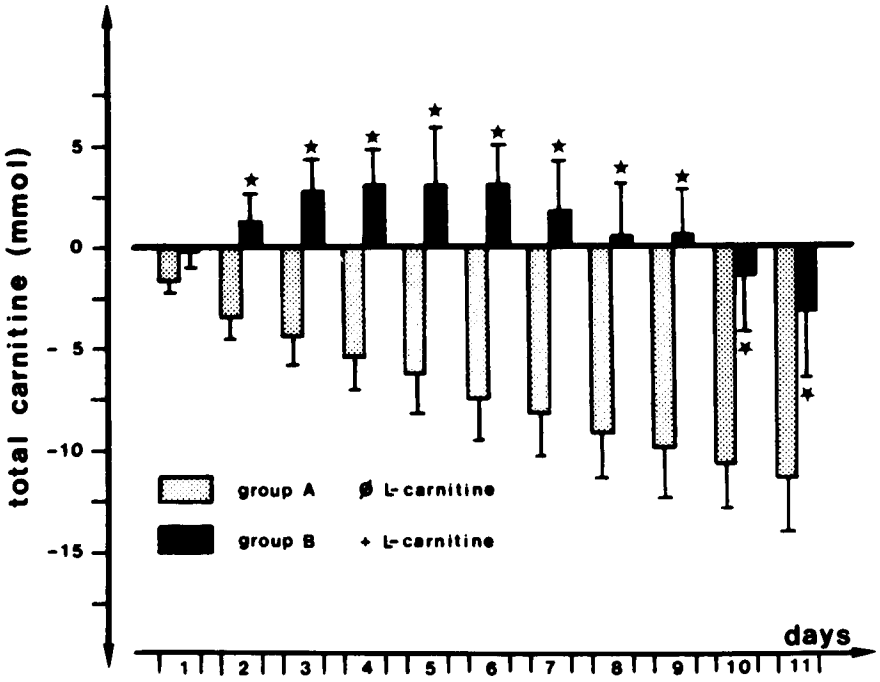

FIG. 1. Postoperative cumulative carnitine balance (mmol) in patients treated with TPN without (group A) and with (group B) carnitine supplementation (mean ± SEM). $P \leq 0.05$ significant *vs* group A.

2.6 mmol of TASC, corresponding to 15.5 ± 3.1% of the initial total body carnitine pool in this group.

The patients in group B show a retention of infused carnitine in the early postoperative period until day 6 (3.1 ± 1.9 mmol; corresponding to 11.1 ± 7.6% of the infused amount). In the later postoperative phase, the retained carnitine is successively excreted, but the cumulative carnitine balance remains slightly positive until day 9 (0.6 ± 2.3 mmol). At the end of the study period, however, all infused carnitine (51 ± 3 mmol) is excreted (55 ± 3 mmol; corresponding to 106.2 ± 7.5% of the infused amount).

Plasma Lipids and Insulin/Glucagon Ratio

Preoperative values fairly conform with those seen in controls (Table VI). No significant differences in the lipid concentrations were observed between the patient groups. Because of fat-containing TPN, the concentrations of TG increase equally in both groups after the operation. After the 3rd postoperative day the concentrations of TG remain almost stable.

Without carnitine supply FFA increase postoperatively, whereas the elevation is not apparent in patients receiving carnitine. Postoperative β-hydroxybutyrate levels in the supplemented group B seem to exceed those observed in group A whereas the insulin/glucagon ratio is noticeably higher during carnitine supplementation.

Indirect Calorimetry

Prior to the operation, EE and RQ, as well as np-RQ, reveal comparable values in groups A and B (Table VII). On day 11, EE and heart rate are elevated to the same extent in both groups whereas the axillary temperatures are similar to the preoperative levels. Neither group show a significant postoperative change in RQ or np-RQ.

Urinary Nitrogen and Cumulative Nitrogen Balance

The preoperative nitrogen losses are similar in groups A and B (8.82 ± 0.94 *vs* 11.00 ± 0.77 g/day) (Fig. 2). The cumulative postoperative nitrogen balance over the entire study period appears to be more favorable in group A than in group B (−20.6 ± 0.6 g *vs* −28. ± 15.0 g).

DISCUSSION

In the majority of earlier investigations carnitine metabolism was evaluated in injured,[6,26-28] burned,[5] and malnourished patients[29,30] receiving short-[5,6,26-28] or long-term[26,29,30], carnitine-free TPN. Only very few studies in adults are dealing with carnitine-supplemented TPN.[31-34]

TABLE VI

Plasma triglycerides, free fatty acids, ketone bodies (μmol/liter) and the insulin/glucagon ratio before and after elective surgery in patients treated with TPN without (group A) and with (group B) carnitine supplementation (Mean ± SEM)

	Triglycerides	Free fatty acids	β-Hydroxybutyrate	Acetoacetate	Insulin/glucagon ratio
Normal values	(870–1560)	(300–700)	(58–170)	(18–78)	(2.5–4.0)
Group A (n = 8)					
Day −1	1297 ± 171	430 ± 103	147 ± 12	31 ± 13	4.18 ± 1.06
Day 1	574 ± 117	371 ± 81	142 ± 27	24 ± 5	3.81 ± 0.82
Day 3	717 ± 132	472 ± 54	148 ± 28	56 ± 20	4.20 ± 0.87
Day 5	1032 ± 120	592 ± 115	134 ± 38	63 ± 35	4.41 ± 1.28
Day 7	1012 ± 158	529 ± 85	226 ± 54	71 ± 29	ND*
Day 9	1063 ± 243	399 ± 74	167 ± 53	31 ± 6	ND*
Day 11	1210 ± 245	543 ± 63	178 ± 34	45 ± 12	6.38 ± 1.33†
Group B (n = 8)					
Day −1	1825 ± 304	461 ± 65	217 ± 43	47 ± 13	5.54 ± 1.39
Day 1	601 ± 74	426 ± 107	168 ± 38	52 ± 9	6.82 ± 2.49
Day 3	1213 ± 215	278 ± 81	251 ± 42	63 ± 8	3.99 ± 0.93
Day 5	1381 ± 185	294 ± 60	277 ± 43	65 ± 13	8.37 ± 3.43†
Day 7	1510 ± 162	360 ± 96	269 ± 57	40 ± 12	ND*
Day 9	1481 ± 167	360 ± 69	279 ± 57	45 ± 13	ND*
Day 11	1354 ± 183	482 ± 75	272 ± 64	40 ± 7	8.45 ± 2.13†

* ND, not determined.

† $p \leq 0.05$ significant *vs* controls.

TABLE VII

Indirect calorimetry measurements before the operation and on the 11th postoperative day in patients treated with TPN without (group A) and with (group B) carnitine supplementation (Mean ± SEM)

	Energy expenditure (kcal/m²·hr)	Respiratory quotient	Nonprotein RQ	Axillary temperature (°C)	Heart rate (beats/min)
Group A (n = 8)					
Day −1	33.7 ± 2.0	0.87 ± 0.04	0.88 ± 0.04	36.9 ± 0.2	60.0 ± 3.2
Day 11	39.2 ± 2.1*	0.86 ± 0.02	0.88 ± 0.03	37.4 ± 0.3	86.2 ± 5.5*
Group B (n = 8)					
Day −1	32.4 ± 2.5	0.84 ± 0.01	0.85 ± 0.02	36.6 ± 0.1	69.2 ± 4.7
Day 11	37.8 ± 3.1	0.85 ± 0.02	0.87 ± 0.03	37.0 ± 0.4	85.8 ± 3.2*

* $p \leq 0.05$ significant *vs* day −1 same group.

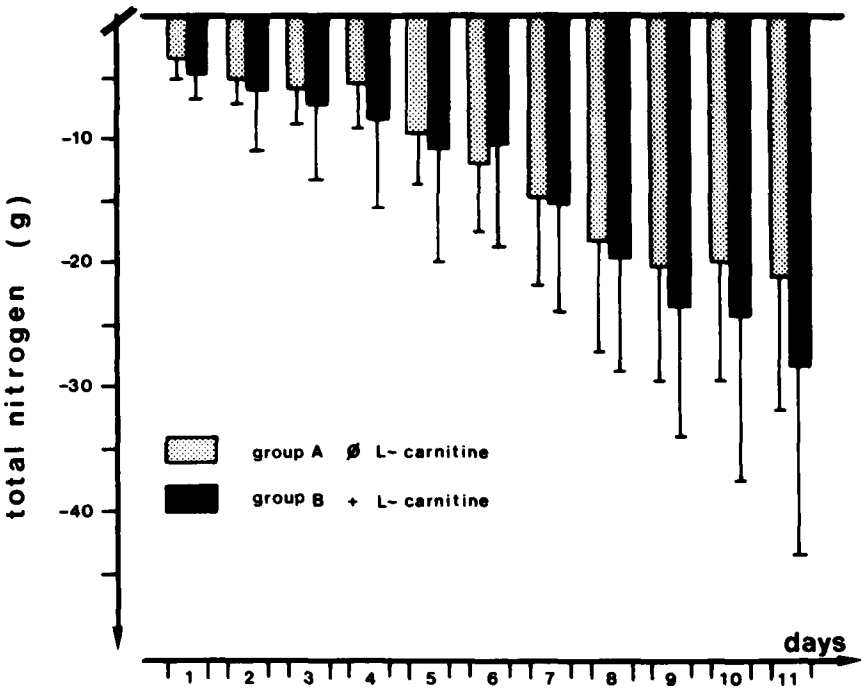

FIG. 2. Postoperative cumulative nitrogen balance (g) in patients treated with TPN without (group A) and with (group B) carnitine supplementation (mean ± SEM).

The present study aimed to evaluate whether carnitine-supplementation during TPN treatment in patients undergoing uncomplicated standard major surgery is associated with appreciable clinical benefits as far as fat and/or nitrogen utilization is concerned.

The patient groups with or without carnitine supplementation were comparable with regard to age, body weight, and sex distribution (Table I). No differences were seen between the tumor staging in the patient groups. No complaints or side effects were recorded in the group of patients receiving carnitine-supplementation.

A mild chronic semistarvation is highly supported by the weight loss of 8.3 ± 2.7 kg measured during a 3-month period preceeding the operation. There is previous evidence that patients with gastrointestinal cancer exhibit diminished muscle mass due to prolonged protein and energy malnutrition.[35-37] Decreased 3-methylhistidine output and negative nitrogen balance[36] as well as enhanced content of extracellular water and sodium[38] appear to be sensitive markers of such a chronic mild semistarvation. Accordingly, in the present patient material the total body carnitine pool was reduced approximately 40% prior to the operation, also suggesting a state of preoperative malnutrition (Table V). Thus, the size of the total body carnitine pool is referred as a further indicator of preoperative malnutrition.

The essential question is to be raised whether the reduced carnitine pool is accompanied by a diminished rate of fat oxidation. An increase in the plasma and urinary ratios of AC/FC and simultaneously enhanced levels of plasma ketone bodies are commonly observed in starvation.[13,39] After exercise an augmented muscular AC/FC ratio was demonstrated.[40] These findings were ascribed to an enhanced but incomplete muscular β-oxidation of FFA. It was speculated that the increase in SCC levels may be a by-product of fatty acid β-oxidation. During the chain shortening of fatty acyl-coenzyme A, incomplete intermediates of β-oxidation could be transported out of the mitochondrias as acylcarnitines to reach the plasma[39] and subsequently might be used for ketone body production in the liver. In the present study, however, the high muscular AC/FC ratio was found to be accompanied by simultaneously decreased AC/FC ratios in plasma and urine. This enrichment of acylgroups in muscle in combination with their suppressed release into plasma may suggest an enhanced but almost complete muscular β-oxidation of FFA, also supported by only moderate elevations in the preoperative concentrations of ketone bodies. Thus, the decreased AC/FC ratios in plasma and urine indicate for an energy-conserving metabolic adaptation as a response to a prolonged moderate energy deficit.

The 3-fold postoperative increase in the total urinary carnitine output in not-supplemented patients (Table IV) is in good accordance with previous reports.[6,27] This considerable urinary carnitine losses are accompanied by only a slight and temporary decrease in the plasma TC concentration, similarly to the observations of Hahn et al.[26] As the majority of infused carnitine is excreted in free form (Table IV), only inconsequential endogenous acylation seems to take place. This finding definitely contrasts to that of Balogh et al[32] and would actually mean that most of the infused free carnitine is not used as carrier for acylgroups. Therefore, it is conceivable to believe that the observed retention of the infused carnitine during the early postoperative period is rather due to a diminished renal excretion than the consequence of an enhanced postoperative demand, especially since the total amount of carnitine supplied is excreted considering the entire study period (Table IV, Fig. 1). In preliminary studies the excretion of LCC was found to be very low in healthy controls and patients (2–4% of the total). Thus, this fraction might be of minor importance for the inter-

pretation of the present study and consequently was not considered.

In the present study no postoperative muscle samples could be obtained. Assuming an uniform distribution of the infused carnitine in the extracellular space[41] the increment in the carnitine pool of this compartment during the early postoperative period can be estimated to be about 0.6 mmol or 20% of the totally retained amount (3.1 mmol until day 6). The reminder 2.5 mmol carnitine may bring about a minute rise in the muscular TC concentration of only approximately 0.1 μmol/g wet weight. Thus, the muscle net uptake of the infused carnitine during the early postoperative period is presumably very low.

The almost stable TG concentration during TPN irrespective of supplementation (Table VI) indicates that the infused LCT are continuously eliminated from plasma. The fact that the maximum level of FFA in group A (Table VI) occurs on the same day as the minimum in the concentration of plasma TC (Table III) points to a transient limited availability of carnitine for FFA transport and oxidation in the early postinjury phase. With regard to ketone bodies, the possible ketogenic effect of carnitine[42-44] could not be confirmed in the present study because of the preoperative differences between the groups and the great variation of the data, although the postoperative ketone body concentrations are higher in patients receiving carnitine supplementation than in those without supply (Table VI). The insulin/glucagon ratio is known to be indicative of the regulation of fat oxidation. An increase in this ratio is accompanied by elevation in the malonyl-coenzyme A concentration which is an inhibitor of carnitine-palmitoyl-transferase I.[43] In contrast to our expectation a trend toward lower lipid oxidation rates on day 11 (data not shown) is observed in the carnitine-supplemented patients which might be due to a higher insulin/glucagon ratio than in patients who received carnitine-free TPN (Table VI).

Mean preoperative EE is 8% higher than that calculated from Harris-Benedict equation.[45] This slight increase might be related either to the presence of carcinoma[46] or to the uncertainty of prediction in this group of patients. The higher EE at the 11th day after operation compared to preoperative values is related to dietary-induced thermogenesis and to a probably residual surgical stress,[47] keeping in mind the possible opposite effect of tumor resection on EE. On the same day, the augmentation of the heart rate is well correlated to the increase in the EE ($r = 0.956$; $p \leq 0.01$) and confirms the enhancement of the metabolic rate. The slightly elevated preoperative RQ observed after an overnight fast might be related to the stressful situation encountered before operation which leads to an increase in pulmonary ventilation and hence RQ. Postoperative RQ is closely related to the RQ of infused nutrients (ie., 0.85). The results failed to show any effect of carnitine supplementation on whole lipid metabolism after 11 days of TPN as also previously reported by Nanni et al[31] for nonseptic patients.

Surprisingly, nitrogen excretion in the carnitine-supplemented patients appeared to exceed that seen in patients without carnitine supply. This observation conforms with the hypothesis of a "threshold" in urinary carnitine elimination. In the present study urinary TASC outputs of 5–6 mmol/24 hr were noted in the supplemented group between 7–11 days after operation (Table IV). Such excessive values might well result in competitive inhibition of amino acid absorption in the proximal renal tubuli. Thus it is concluded that the infused amount of carnitine (12 mg/kg·day) was possibly too high to facilitate physiological renal handling of this solute.

It is concluded that the usefulness of carnitine supplementation during postoperative TPN was not apparent in this present study. Further studies, presumably with lower carnitine doses, are warranted to explore the clinical benefit of carnitine supplementation in pathological conditions requiring long-term TPN.

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