

Original Article

Carnitine depletion during total parenteral nutrition despite oral L-carnitine supplementation

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Abstract

Carnitine (CAR) plays an important role in the β -oxidation of fatty acids. Less attention, however, has been paid to CAR compared to other nutrients even in total parenteral nutrition (TPN). To examine CAR metabolism during TPN and the effect of simultaneous oral L-CAR supplementation on CAR levels, the blood CAR level was measured in a 3-year-old boy receiving long-term TPN because of short bowel syndrome. Both the total and acyl CAR in the serum were evaluated under various nutritional conditions including oral supplementation of L-CAR. Low CAR concentrations were observed especially when lipid containing TPN regimens were in place. Oral L-CAR supplementation was not sufficient to restore the low CAR levels in the present index patient even when the dose was increased to 120 mg/kg in accordance with the result of the L-CAR absorption test that revealed poor intestinal absorption of this nutrient. Moreover, a markedly low CAR level was measured during the onset of sepsis in the patient, and the blood CAR was depleted when lipid metabolism was activated by lipid loading or sepsis. To date, the late effects of CAR depletion on child growth have not been well examined. It is recommended that the blood CAR level be maintained at normal levels before any prominent manifestations of the deficiency have developed. The intravenous administration of CAR appears to be necessary to supply a sufficient amount of CAR for patients with severe malabsorption.

Key words carnitine, short bowel syndrome, total parenteral nutrition,

Carnitine (CAR), one of the nutrients supplied mainly from meat and dairy products, is an essential cofactor for many metabolic interactions in the body.^{1,2} There are two chemical forms of CAR, L-CAR and D-CAR, of which L-CAR is biologically active and is pharmaceutically available for medical indication. In the body, a portion of CAR binds fatty acids forming acyl (A) CAR while the rest exists as free (F) CAR. The sum of these two fractions is referred to as total (T) CAR. Some of its physiological roles in fatty acid oxidation and in the excretion of organic acids have been well investigated.

In the former, palmitoyl carnitine synthetase I of the mitochondria membrane facing the cytosol facilitates the formation of A CAR from CAR and fatty acid. Acylcarnitine can enter the mitochondrion with the aid of acylcarnitine translocase. Palmitoyl carnitine synthetase II, an enzyme present in the inner membrane of the mitochondria, then cleaves acylcarnitine to fatty acid and F CAR. As a result, CAR conveys fatty acids into the inner compartment of the mitochondria where adenosine triphosphate (ATP) is generated from fatty acids by β -oxidation.

The function of CAR to excrete an excess amount of organic acids upon their precipitation in the body was clearly demonstrated in organic acidemia such as propionic acidemia and methylmalonic aciduria. Organic acids precipitated in the mitochondria form acyl-coenzyme A (CoA), which may be harmful because of the disturbance in the balance of the ratio between acetyl and acyl-CoA in the mitochondria. Carnitine, in this situation,

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accepts organic acid from the corresponding acyl CoA. Carnitine facilitates the excretion of organic acids from the mitochondria by the reverse sequence of the reaction for the influx of fatty acids described perviously.

Besides these well recognized functions of CAR, the list of possible physiological roles of CAR has expanded dramatically during the last decade. The disorders included in this list are chronic fatigue syndrome,³ cardiomyopathy,⁴⁻¹¹ muscle weakness in hemodialysis¹² and Reye syndrome.^{13,14} Contrary to the recent recognition of the relevance of CAR in physiological metabolism and in therapeutic as well as prophylactic usage against a wide variety of disorders,¹⁵ the role of CAR as a nutrient has not received sufficient attention. This also occurs in total parenteral nutrition (TPN) when the proper supply of nutrients needs to be monitored. The reasons predicted for this indifference might be that CAR can be synthesized *de novo* from other amino acids such as lysine and methionine^{1,16,17} and that endogenous CAR is believed to be theoretically sufficient to cover the demands of CAR in adulthood.¹⁸ At this point in time, CAR is categorized nutritionally as a non-essential nutrient. In addition, the symptoms solely attributed to exogenous CAR deficiency have rarely been reported.¹⁹⁻²² Therefore, the supplementation of CAR is considered only when TPN is given to premature babies whose CAR consumption by the body can exceed their intake. In general, the supplementation of CAR as a nutrient is not an established indication in TPN.

In the present study, the blood level of CAR was monitored in a pediatric patient who has a severe impairment of the absorption of whole nutrients including CAR because of short bowel syndrome. The effect of oral supplementation of CAR was also evaluated.

Patient report

A boy was born at 34 weeks gestation with an Apgar score of 8 in a regional hospital. Immediately after birth, he developed respiratory distress and was diagnosed as transient tachypnea of the newborn. On day 7 of life, he vomited frequently and his abdomen distended markedly. His abdominal X-rays revealed pneumatosis intestinalis expanding to include within the whole intestine including the stomach, suggesting that he had severe necrotizing enterocolitis. On the same day, he was transferred to the neonatal intensive care unit (NICU) of Fukuoka University Hospital and underwent an emergency operation. During surgery, in accordance with the X-ray findings, his stomach, duodenum, jejunum and ileum were found to have subserous gas and severe necrosis was observed in

the jejunum and ileum. One of our members, ZS, resected his jejunum and ileum leaving the duodenum and the end of the ileum where necrosis was not evident. After the second operation, his remaining small bowel was composed of a short portion of the terminal ileum. Since then he has been on TPN. The use of TPN continues at home during the night hours. Meals are given freely. The TPN regimens utilized during the present study are shown in Table 1. The physical characteristics and major laboratory data of this patient are also shown in Table 1. Although he showed short stature as a result of frequent TPN catheter troubles in infancy, his growth rate and psychomotor development were found to be within the normal range when the study was carried out. A xylose absorption test was performed in which the blood xylose concentration 1 h after ingestion of 0.5 g/kg of xylose was

Table 1 Standard nutrient regimen, laboratory data and physical characteristics for the patient

Standard nutrient regimen	(Cyclic nocturnal TPN)
Volume	1000 mL
Total calories	860 kcal
Aminic [®] (Roussel-Morishita Co., Tokyo, Japan)	200 mL
Elemenmic [®] (Roussel-Morishita Co.)	1/3A
Otsuka MV [®] (Otsuka Pharmaceutical Co., Tokyo, Japan)	1 set
Lipid administration 20% Intralipos (The Green Cross Co., Osaka, Japan)	(DIV with TPN) 0.6 g/kg per day
Laboratory data	
WBC 8000/ μ L	Total cholesterol 146 mg/dL
Lymphocytes 56.0%	Triglyceride 59 mg/dL
T cell 54%	Free fatty acid 1.02 mEq/L
B cell 36%	
RBC 423×10^4 / μ L	Transferrin 240 mg/dL
Hb 12.8 g/dL	Prealbumin 17.9 mg/dL
Plt 14.6×10^4 / μ L	Retinol binding protein 3.8 mg/dL
TP 6.5 g/dL	Fe 31 μ g/dL
Alb 4.3 g/dL	Zn 62 μ g/dL
GOT 29 IU/L	Ferritin 206 ng/mL
GPT 19 IU/L	Glucose 101 mg/dL
LDH 537 IU/L	NH ₄ 35 μ mol/L
Physical characteristics	
Height 83.3 cm (-2.7 SD)	
Weight 11.4 kg (-1.4 SD)	
Chest circumference 48.7 cm (-1.1 SD)	
Head circumference 49.4 cm (-0.1 SD)	

8 mg/dL (control ≥ 25 mg/dL).²³ The total xylose excreted in the urine during a 5 h test period was 115 mg representing 1.80% of the ingested xylose (control 3–6 years, 17.5–37%; mean, 25.6%). This test verified the impaired absorption within the remaining small intestine.

Carnitine measurement

Carnitine levels were determined in a COBAS FARA automatic analyzer (Hoffman-La Roche Ltd, Basel, Switzerland) by an enzyme cycling method. This method measures the increase in absorbance at 415 nm of thio-reduced nicotinamide adenine dinucleotide (NADH) produced by enzyme cycling reactions initiated with CAR dehydrogenase (EC 1.1.1.108). The T and F CAR concentrations were assayed separately with and without the addition of A CAR esterase, respectively.²⁴ The A CAR was calculated from the difference between T and F CAR. The reagents for the measurement were purchased as a kit from Kainos Laboratories Inc., manufactured by Asahi Kasei Chemical Industrial Co., Tokyo, Japan. Blood was obtained 2 h after the termination of daily TPN when breakfast was given. For blood CAR measurement, the undiluted serum was used. The patient's urine was diluted to one-tenth with physiological saline for the determination of urinary CAR with correction for urinary creatinine. Samples were stored at -20°C until the time of measurement.

The normal values of blood and urinary CAR concentration corresponding to the patient's age were established by obtaining 50 randomly collected urine and blood samples from outpatients who visited the clinic with minor illnesses such as upper respiratory tract infections etc. The age of this population ranged from less than 1 year to 6 years old, with a mean of 3.1 ± 1.6 years. Children appearing undernourished were excluded. These randomly selected subjects did not include any individuals who were thought to have a predisposing factor for CAR depletion; that is, patients treated with drugs that increase CAR excretion such as valproate or antibiotics with a pivoxyl base. Any patients with organic acidemia were not included in the sample population.

Carnitine absorption test

A carnitine absorption test was performed according to Rizza *et al.*²⁵ Before the test, CAR supplementation had been discontinued for 12 weeks. The patient fasted for 6 h prior to the test and the fasting state continued for five additional hours after the administration of 100 mg/kg of L-CAR. Blood was obtained from an indwelling arterial catheter at 0, 1, 3, 5, 7, 12 and 24 h after the administration.

Urine was excreted completely before the test, then collected throughout the test and pooled for measurement of the total amount of CAR excreted in the urine throughout the test. Serum CAR concentrations minus the value at the zero point or the endogenous value were compared to the corresponding published reference figures.²⁵

Results

To determine whether the blood CAR level of this patient was maintained in a comparable range to the standard and to evaluate the effect of nutritional regimens given and also to measure the effect of oral L-CAR supplementation on the blood CAR level, the concentration of serum CAR was measured under four different nutritional conditions. Each consisted of different combinations of intravenous lipid administration and oral L-CAR supplementation. The details of the different trials were as follows: (i) TPN consisted of a standard high caloric alimentation regimen such as glucose, amino acids, vitamins and trace elements as indicated in Table 1, but the TPN did not contain intravenous lipid administration. L-CAR supplementation was omitted for this condition; (ii) the same as (i) but 60 mg/kg per day of L-CAR was given orally divided into three equal doses; (iii) the TPN regimen contained 0.6 g/kg per day of 20% lipid emulsion; and (iv) the same as (iii), but in addition, L-CAR was supplied orally in three equal doses. Each nutritional regimen was maintained for at least 10 consecutive days before the blood sampling. The laboratory data assessing his nutritional state during each nutritional trial showed no significant change in CAR levels throughout the test. The venous blood was drawn 3 h after the termination of nocturnal TPN when breakfast occurred and a dose of L-CAR might be given.

As in Table 2, compared to the standards that are 53.9 ± 12.5 $\mu\text{mol/L}$ for total CAR and 17.1 ± 9.6 $\mu\text{mol/L}$ for A CAR, the total and A CAR levels of the index patient were significantly lower irrespective of the nutritional conditions. Since both the A and T CAR were lowered equivalently in the present case, the ratio between A and T CAR was maintained in the normal range. When the effect of administration of lipid emulsion on the metabolism of CAR was evaluated during trials (iii) and (iv), lower levels of CAR were observed compared to those during the lipid-free nutritional trials, (i) and (ii). These decreased CAR levels are indicative of CAR consumption by lipid metabolism. Despite oral L-CAR supplementation, the CAR level was not restored to the normal range, indicating that the oral L-CAR supplementation was not sufficient at this dose.

Table 2 Carnitine concentrations under different nutritional conditions

	I	II	III	IV	Standard
T CAR ($\mu\text{mol/L}$)	31.5	30.0	27.1	18.9	53.9 ± 12.5
A CAR ($\mu\text{mol/L}$)	9.4	7.8	7.4	5.9	17.0 ± 9.1
A CAR/ T CAR	0.30	0.26	0.27	0.31	0.31 ± 0.15

I, Total parenteral nutrition (TPN) without lipid; II, I + L-CAR (60 mg/kg per day); III, TPN with lipid (0.6 g/kg per day); IV, III + L-CAR (60 mg/kg per day).

T CAR, serum total carnitine; A CAR, serum acyl carnitine.

Table 3 High-dose L-carnitine supplementation

	Dose			Standard	
	60	90	120		
T CAR ($\mu\text{mol/L}$)	30.0	39.5	38.5	22.0*	53.9 ± 12.5
A CAR ($\mu\text{mol/L}$)	7.8	15.4	16.0	3.6*	17.1 ± 9.2
A CAR/T CAR	0.26	0.39	0.42	0.16*	0.31 ± 0.15

*Sepsis.

T CAR, Serum total carnitine; A CAR, serum acyl carnitine.

The relationship between the blood CAR level and the dose of L-CAR given orally was evaluated for the patient as shown in Table 3. As the dose of L-CAR was increased from 60 to 120 mg/kg, both T and A CAR levels were measured under the nutritional conditions corresponding to trial III described previously. This trial (iii) did not include intravenous lipid administration. Despite increasing the oral dose, the blood level of CAR did not increase accordingly. During the present study, the lowest blood level of CAR was recorded, unexpectedly, at the time when the highest dose of L-CAR was supplied. At that time, the patient showed lethargy, frequent bouts of vomiting and high fever suggesting sepsis that was confirmed by a concomitant positive blood culture reported later. In this situation, the depletion of A CAR was significant so that the ratio between A and T CAR was decreased. This episode suggested that during accelerated catabolism in conditions such as sepsis or injury, CAR depletion could be increased. This depletion did not appear to be corrected by high doses of oral L-CAR supplementation for the present patient.

Absorption of L-CAR by the patient was assessed with serum and urinary CAR values following oral administration of 100 mg/kg of L-CAR. As shown in Fig. 1, the

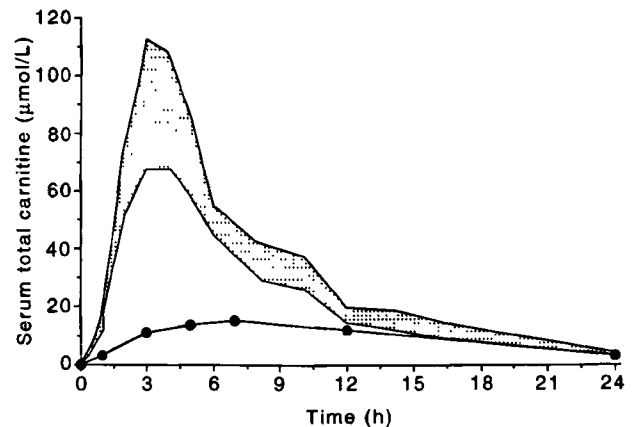


Fig 1. Blood was obtained at 0, 1, 3, 5, 7, 12 and 24 h after the oral administration of 100 mg/kg of L-carnitine (L-CAR). The serum total CAR concentrations were determined. The CAR concentrations minus the value at the zero point or the endogenous value (●) were compared to published reference values (shaded area).²⁵

plasma concentration profile as a function of time minus endogenous values was much lower than the corresponding reference values. Poor absorption of this nutrient was validated by the small amount of total excreted CAR in the urine during the test. The T CAR excreted in the pooled urine during the test was 78 μmol or merely 1.3% of the supplemented CAR. Normally, CAR can be observed in the urine even without CAR loading. Therefore, the actual fraction of excreted CAR in the urine of the present patient should be considered less than 1.3% of the supplemented carnitine.

Discussion

In the present study, low blood CAR levels were observed in a 3-year-old patient who had been on long-term TPN because of short bowel syndrome. The jejunum of the patient had been excised. The jejunum is known to be a main site for the absorption of dietary CAR; therefore, exogenous CAR could be predicted to be poorly absorbed.^{26,27} The aminogram evaluated during the study showed normal concentrations of lysine and methionine (data not shown), both of which are precursors for endogenous CAR^{16,17} and indicative of a sufficient substrate for the *de novo* synthesis of CAR. The absorption test for CAR without any noted loss of CAR in the urine clearly demonstrated that the low blood CAR in the patient resulted from the malabsorption of exogenous CAR. As it is known that the concentration of CAR in the blood

reflects the total storage of CAR in the tissue, the low blood CAR implied total systemic depletion of CAR in the patient.²⁸

Although there were no manifestations of hypoglycemia without ketone body production that could be solely attributed to CAR depletion, liver steatosis and hyperammonemia observed in the patient should be addressed as a possible symptom of CAR depletion. The finding of a fatty liver had been noted on ultrasound tomography in the patient for the past 2 years. Because steatosis is one of the typical symptoms of impairment of CAR metabolism reported from extensive animal model studies, CAR depletion might have precipitated the fatty liver in the present patient. However, the relationship between fatty liver and low CAR level in the present case remains unclear because the diagnosis had not been confirmed by liver biopsy. It is also well known that TPN *per se* frequently creates a complication of steatosis. The patient suffered from hyperammonemia ranging from 48 to 543 $\mu\text{mol/L}$ several times prior to the study and this was a motivating factor for the monitoring of his CAR level. The concentrations of CAR during these episodes of hyperammonemia, unfortunately, were not documented. The fact that no other factor responsible for hyperammonemia was found strongly suggested that CAR depletion initiated mitochondria dysfunction in the area of urea metabolism.

A noteworthy finding of the present study is the exacerbation of low blood CAR by the loading of intravenous lipid emulsion or by the occurrence of sepsis. For lipid metabolism, CAR is an essential cofactor to traffic fatty acids between the mitochondrial inner compartment and the cytosol. During this process, CAR can be reduced if its storage is insufficient or its consumption exceeds the requirement for fielding fatty acids. In the present patient, the CAR supply that could be utilized for lipid metabolism must have been strictly limited so that even the relatively low dose (0.6 g/kg) of lipid might have accelerated CAR depletion. The same mechanism presumably was involved in the considerable CAR depletion documented during the episode of sepsis. Thus, the catabolism developed during sepsis moved fatty acids out of the adipose tissues and the β -oxidation was activated by lipid loading. Intravenous lipid administration is established as routine and necessary in TPN alimentation. Also, sepsis related to catheter infection is conceded to be one of the most frequent complications of TPN. The CAR depletion noted in both circumstances, therefore, should be considered in every pediatric patient on long-term TPN. Organic aciduria or acyl CoA dehydrogenase deficiency with significant symptoms can result with lipid loading or infection.

In addition to the pathophysiology of CAR depletion predicted on the basis of the well known functions of CAR, other concerns emerge regarding the late adverse effects of CAR insufficiency. Novel physiological and prophylactic roles of CAR have been recognized. Some of the putative roles of CAR currently highlighted, encompass a wide variety of disorders from cardiomyopathy to chronic fatigue syndrome. The effects of CAR on child growth, however, have not been well studied.^{21,29} In other words, the question still remains as to whether chronic CAR depletion with levels that do not create acute symptoms will affect pediatric patients during future years.

Supplementation of CAR for patients on long-term TPN beyond the neonatal period is still controversial. Currently L-CAR supplementation is believed to be unnecessary in TPN with the exceptions being premature neonates and severely injured patients. The main reason for this might come from the assumption that endogenous CAR, based upon its metabolism, is theoretically supposed to be sufficient to cover the physiological requirement even if the absorption of exogenous CAR is impaired. This may not be the case, however, for infants in whom the activity of the hepatic g-butyrobetaine hydroxylase, a CAR generating enzyme, is low.³⁰ Another reason for the reluctance to supply this nutrient during TPN might have emerged from the fact that CAR deficiency during TPN has rarely manifested symptoms, although low levels of blood CAR have been observed.

Some attempts, therefore, have been made to detect the adverse effects of CAR depletion during TPN utilizing the major functions of CAR described in the present paper as an indicator. Fatty acid metabolism in which CAR is closely involved is believed to be the most useful indicator for the evaluation. Although the concentration of free fatty acids and ketone bodies were reportedly normal regardless of intravenous CAR supplementation in some studies,^{31,32} favorable effects, in contrast, were observed on the same parameters when the analyses were carefully performed following reduction of co-administered glucose or during a fasting challenge.³³⁻³⁶ Even these parameters are not sufficient to depict correctly the whole machinery of fatty acid metabolism or to detect any other adverse effects of CAR depletion. Moreover, it has been reported that hypoglycemia without ketogenesis or hyperammonemia are not seen routinely in chronic CAR deficiency. A lack of these representative symptoms indicative of CAR depletion during TPN may be explained as follows. As it is known that the human body is a large storehouse of CAR (i.e. in the muscles), the manifestation of acute depletion of CAR as seen in congenital CAR deficiency may not be manifested as readily when CAR depletion slowly progresses during TPN.

In other words, a paucity of the adverse effects of CAR depletion that are detectable by conventional methods does not necessarily support the theory that CAR supplementation would be unnecessary for this population. In fact, several studies suggest that nitrogen metabolism and growth are promoted by CAR.^{29,36,37} When pediatric patients have severe malabsorption, they can be threatened by CAR depletion and are vulnerable to the metabolic consequences resulting from this deficiency. The principle of TPN (e.g. all nutrients must be properly supplied) should dictate the choice of the nutrients in TPN. It is recommended, therefore, that attempts to restore blood CAR levels be made during TPN for pediatric patients at least until the influence of chronic CAR insufficiency has been well investigated and reported.

In the supplementation of L-CAR for patients on long-term TPN, especially for patients with short bowel syndrome, a more practical problem arises. As was clear in the present case, oral supplementation of L-CAR cannot provide a sufficient amount of CAR when patients have severe malabsorption. For this population, intravenous supplementation should be considered. However, the availability of L-CAR for intravenous administration is limited. Even when available, L-CAR for intravenous use is approved only for cardiomyopathy and not for the supplementation of TPN. This problem is of importance because L-CAR itself is categorized as an orphan drug that is necessary but limited in its use. Therefore, it may take time and more research before the intravenous use of L-CAR during TPN is approved. It is urged that the study of CAR as a nutrient should be extensively carried out to promote expanding the indications for the use of L-CAR, as well as approval of its intravenous administration.

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