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Carnitine Deficiency and Improvement of Muscle Cramp by Administration of Carnitine in Patients with Liver Cirrhosis

Naoki Hotta

Department of Internal Medicine, Division of Hepatology, Masuko Memorial Hospital, Aichi, Japan
Email: hotta4166@yahoo.co.jp

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Abstract

Aim: We measured carnitine levels in patients with carnitine including dialysis patients, and examined whether administration of L-carnitine improved muscle symptoms. Methods: We measured carnitine levels in 27 patients with liver cirrhosis who were receiving treatment in our hospital, and administered L-carnitine (600 mg - 1800 mg) to patients having muscle cramps for approximately one month and examined the presence/absence of the symptom. We measured carnitine concentration before and after dialysis, before dialysis after the administration to eight dialysis patients, before and after the administration to 19 nondialytic patients. Results: The total carnitine levels before the dialysis of dialysis patients were an average of 42.2 μmol/L and fell to 17.7 μmol/L after more dialysis, but it was increased to 155 μmol/L after the administration of L-carnitine. In the nondialytic patients, the total carnitine levels were significantly increased from 71.7 μmol/L to 101.7 μmol/L after the administration of L-carnitine (P = 0.038). For symptomatic patients, significant improvement of muscle clamps was observed in the L-carnitine administrated group when compared with the non-administrated group (P = 0.0002). Conclusions: Total carnitine levels were low even before dialysis in the dialysis patients with liver cirrhosis in particular and they further decreased after the dialysis. Administration of L-carnitine increased the total carnitine levels and improved the symptom. Based on these results, we conclude that L-carnitine is useful for carnitine deficiency in patients with liver cirrhosis.

Keywords

Carnitine, Liver Cirrhosis, Dialysis Patient

1. Introduction

In recent years, we occasionally come across some reports that carnitine is useful for improving blood ammonia

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and cognitive function in hepatic cirrhosis patients with latent hepatic encephalopathy [1]-[3]. Recently, levo-carnitine chloride (L-Cartin® tablets 100 mg, 300 mg: Otsuka Pharmaceutical Co., Ltd., hereinafter referred to as LC) has also become available in Japan as a pharmaceutical agent for patients suspected of having carnitine deficiency. We measured serum carnitine concentrations in hepatic cirrhosis patients including dialysis patients and examined whether their cramps improved or not. Muscle spasms and hypotension during dialysis, atrophy of skeletal muscles and decrease in exercise capacity, anemia, and reduced cardiac function associated with decreased carnitine levels in dialysis patients have been reported [4]-[6]. Whereas a majority of the reports on the utility of carnitine have used supplements, we used LC for this investigation.

2. Methods

2.1. Patients

This was a randomized, double-blind, placebo-controlled study.

The serum carnitine concentrations in 27 patients with hepatic cirrhosis who are outpatients at our hospital were measured by using the enzyme cycling method (total carnitine reference value 45.0 - 91.0 μmol/L, free carnitine reference value 36 - 74 μmol/L, acylcarnitines reference value 6 - 23 μmol/L). LC (600 - 1800 mg) was administered to patients with cramps for 1 month, and the presence or absence of the symptom was examined. Serum carnitine concentrations were measured before and after dialysis and after LC administration in 8 dialysis patients, and before and after administration in 19 non-dialysis patients. In 17 patients with the symptom, the serum carnitine concentrations following administration were measured 1 month later. The study was reviewed and approved by the ethics committee established in the Masuko Memorial Hospital. The patients were given explanation on the study, for which written consents were obtained.

The 27 patients consisted of 8 dialysis and 19 non-dialysis patients, with no differences in the background factors (age, sex, cause, Child-Pugh grade, complication by liver cancer, implementation of dialysis, and with or without administration of branched-chain amino acids, hereinafter referred to as BCAAs, formulation) between the two groups. A significant difference was noted in serum total carnitine concentrations (**Table 1**). A significant difference was observed in serum total carnitine concentration between the dialysis patients prior to dialysis and the non-dialysis patients (42.2 ± 19.5 μmol/L vs. 70.5 ± 20.7 μmol/L, $P = 0.004$) (**Figure 1**). In the present study, cramps, one of the symptoms experienced by patients with hepatic cirrhosis, developed in 67% (18 of 27 patients) of the patients, consisting of 50% (4 of 8 patients) of the dialysis patients and 74% (14 of 19 patients) of the non-dialysis patients (**Table 2(a)**). The administration of LC caused the cramps to disappear in 92% (12 of

Table 1. The 27 patients consisted of 8 dialysis and 19 non-dialysis patients, with no differences in the background factors (age, sex, cause, Child-Pugh grade, complication by liver cancer, implementation of dialysis, and with or without administration of branched-chain amino acids, hereinafter referred to as BCAAs, formulation) between the two groups. A significant difference was noted in serum total carnitine concentrations.

Baseline participant characteristics			
	Hemodialysis n = 8	Non-hemodialysis n = 19	*P* value
Age mean ± S.D.	62 ± 11	66 ± 9	0.32*
Sex male/female	5/3	12/7	1.00**
Etiology (Alco/HBVHCV//nonBnonC/other)	0/0/7/0/1	6/2/10/1/2	0.10**
Child-pugh grade (A/B/C)	4/4/0	10/5/4	0.38**
Child-pugh score mean ± S.D.	6.5 ± 1.2	7.1 ± 2.7	0.43**
HCC complication (%)	7 (88)	12 (63)	0.36**
Total-carnitine mean ± S.D. μmol/L	42.2 ± 19.5	70.5 ± 20.7	0.004*
BCAA treatment (%)	4 (50)	11 (58)	1.00**
L-carnitine treatment (%)	5 (63)	11 (63)	1.00**
Cr mean ± S.D. mg/dL	8.9 ± 2.8	0.9 ± 0.4	<0.0001*

*Student's t test; **Fisher's exact test.

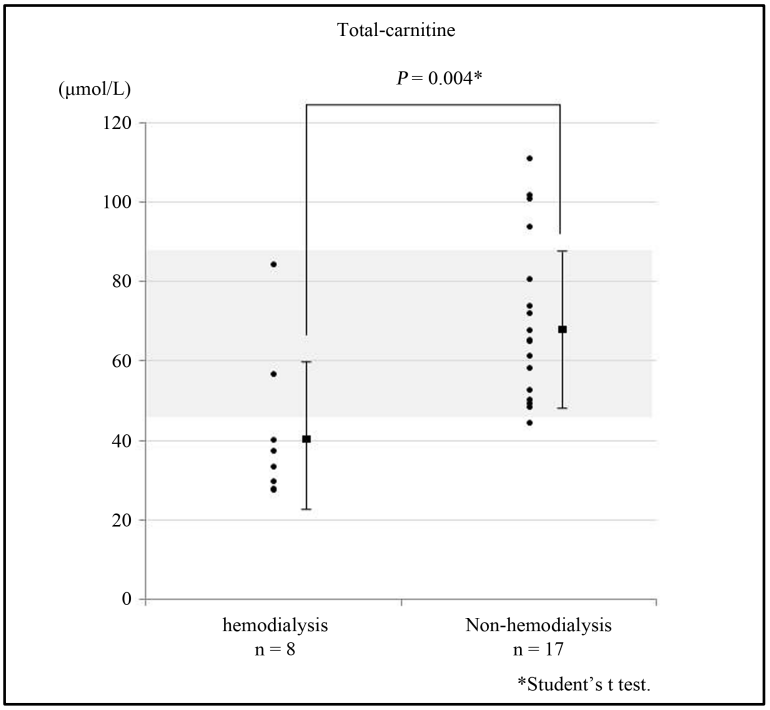

Figure 1. A significant difference was observed in serum total carnitine concentration between the dialysis patients prior to dialysis and the non-dialysis patients (42.2 ± 19.5 μmol/L vs. 70.5 ± 20.7 μmol/L, $P = 0.004$).

13 patients) of the patients, while the symptom did not disappear in the absence of LC administration, showing a significant difference between the two groups ($P = 0.0002$) (**Table 2(b)**).

2.2. Statistical Analysis

With respect to test methods, the paired t-test and Student's t-test were used for paired continuous variable data and unpaired continuous variable data, respectively, and the chi-square test or the Fisher's exact test was used for categorical variable data. All tests were two-sided, and difference levels of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Dialysis Patients

The total carnitine concentration of 6 dialysis patients whose serum carnitine concentrations were measured was a subnormal 42.2 ± 19.5 μmol/L before dialysis and 17.7 ± 6.5 μmol/L after dialysis, showing significant decrease ($P = 0.011$). Free carnitine levels decreased significantly from 27.0 ± 13.2 μmol/L before dialysis to 11.2 ± 25.4 μmol/L after dialysis ($P = 0.009$); acylcarnitine levels decreased significantly from 15.2 ± 6.2 μmol/L to 5.8 ± 1.9 μmol/L ($P = 0.021$) (**Figure 2**). In 5 patients treated with LC, the levels of serum total carnitine, free carnitine, and acylcarnitine before and after administration increased significantly from 42.0 ± 24.3 μmol/L to 155.0 ± 114.8 μmol/L, 26.4 ± 15.3 μmol/L to 102.9 ± 80.1 μmol/L, and from 16.8 ± 10.1 μmol/L to 60.8 ± 34.3 μmol/L (**Figure 3**).

3.2. Non-Dialysis Patients

In the non-dialysis patients, no significant differences was observed in patient backgrounds (age, sex, cause, Child-Pugh grade, complication by liver cancer, total carnitine concentration, and with or without BCAAs administration) between the LC group of 12 patients and non-administration group of 7 patients. By Child-Pugh grades, serum total carnitine showed little variation (grade A, 67.4 ± 20.4 μmol/L; grade B, 51.6 ± 18.8 μmol/L;

Table 2. Cramps, one of the symptoms experienced by patients with hepatic cirrhosis, developed in 67% (18 of 27 patients) of the patients, consisting of 50% (4 of 8 patients) of the dialysis patients and 74% (14 of 19 patients) of the non-dialysis patients **(a)**. The administration of LC caused the cramps to disappear in 92% (12 of 13 patients) of the patients, while the symptom did not disappear in the absence of LC administration, showing a significant difference between the two groups (P = 0.0002) **(b)**.

(a)

Incidence on muscle cramp				
	Total patients n = 27	Hemodialysis n = 8	Non-hempdialysis n = 19	P value
Muscle cramp (%)	18 (67)	4 (50)	14 (74)	0.3748

(b)

Improvements on muscle cramp			
	L-carnitine n = 13	Non-L-carnitine n = 4	P value
Disappearance of muscle cramp (%)	12/13 (92)	0/4 (-)	0.0002*
Hemodialysis	3/3 (100)	0/1 (-)	0.2500
Non-hemodialysis	9/10 (90)	0/3 (-)	0.0140*

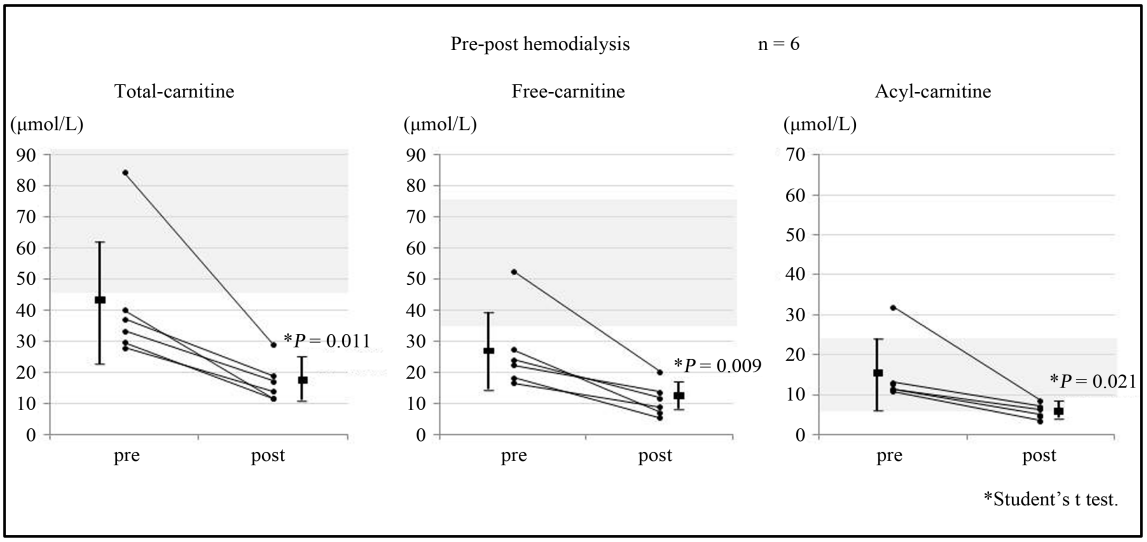

Figure 2. The total carnitine concentration of 6 dialysis patients whose serum carnitine concentrations were measured was a subnormal 42.2 ± 19.5 μmol/L before dialysis and 17.7 ± 6.5 μmol/L after dialysis, showing significant decrease (P = 0.011). Free carnitine levels decreased significantly from 27.0 ± 13.2 μmol/L before dialysis to 11.2 ± 25.4 μmol/L after dialysis (P = 0.009); acylcarnitine levels decreased significantly from 15.2 ± 6.2 μmol/L to 5.8 ± 1.9 μmol/L (P = 0.021).

grade C, 71.6 ± 28.1 μmol/L); free carnitine also exhibited little variation (grade A, 51.6 ± 16.8 μmol/L; grade B, 56.3 ± 10. 9 μmol/L; grade C, 55.0 ± 18.9 μmol/L); and acylcarnitine also showed little variation (grade A, 15.8 ± 8.9 μmol/L; grade B, 18.3 ± 9.9 μmol/L; grade C, 16.6 ± 10.5 μmol/L), neither of which showed a significant difference (**Figure 4**). In 12 patients treated with LC, the serum total carnitine levels before and after administrations increased significantly from 71.7 ± 22.8 μmol/L to 101.7 ± 45.5 μmol/L (P = 0.038); free carnitine increased significantly from 54.9 ± 15.4 μmol/L to 84.4 ± 36.2 μmol/L (P = 0.012); and acylcarnitine increased from 16.8 ± 9.1 μmol/L to 17.3 ± 9.8 μmol/L, showing an upward trend (**Figure 5**). Since no improvement was observed in 1 LC-treated case (cramps developed several times monthly), the dose of LC was increased, and consequently the symptom was improved 1 month later.

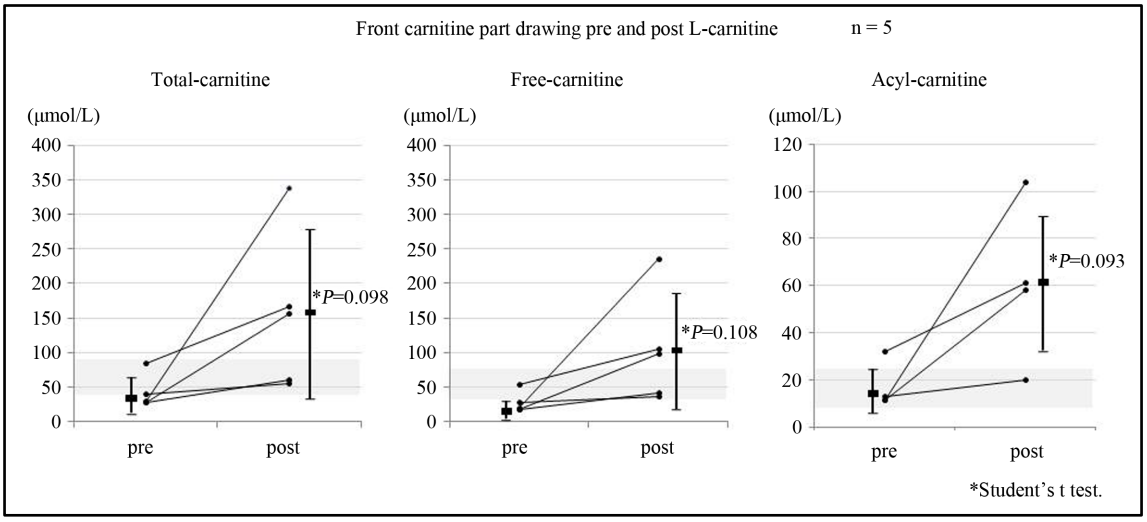

Figure 3. 5 patients treated with LC, the levels of serum total carnitine, free carnitine, and acylcarnitine before and after administration increased significantly from 42.0 ± 24.3 μmol/L to 155.0 ± 114.8 μmol/L, 26.4 ± 15.3 μmol/L to 102.9 ± 80.1 μmol/L, and from 16.8 ± 10.1 μmol/L to 60.8 ± 34.3 μmol/L.

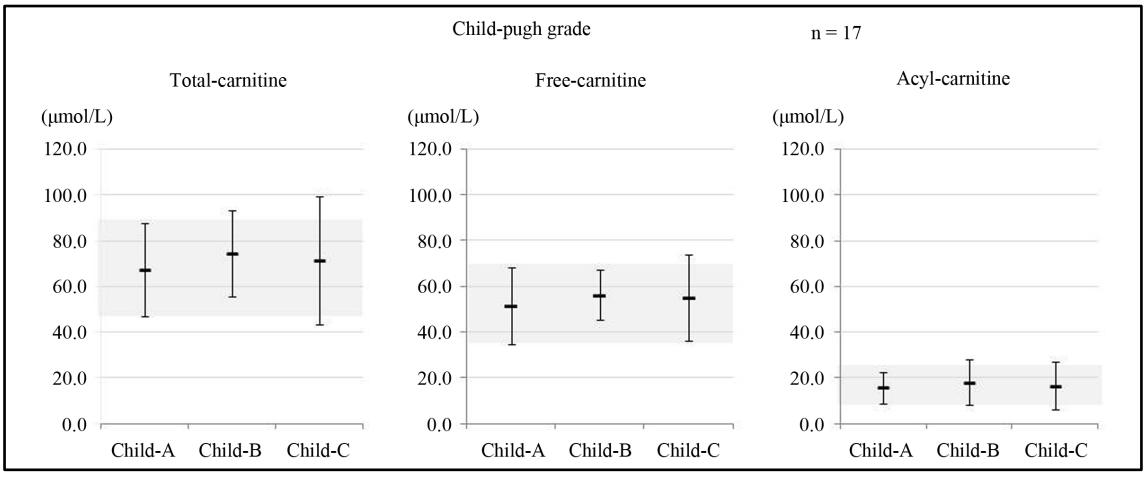

Figure 4. Child-Pugh grades, serum total carnitine showed little variation (grade A, 67.4 ± 20.4 μmol/L; grade B, 51.6 ± 18.8 μmol/L; grade C, 71.6 ± 28.1 μmol/L); free carnitine also exhibited little variation (grade A, 51.6 ± 16.8 μmol/L; grade B, 56.3 ± 10. 9 μmol/L; grade C, 55.0 ± 18.9 μmol/L); and acylcarnitine also showed little variation (grade A, 15.8 ± 8.9 μmol/L; grade B, 18.3 ± 9.9 μmol/L; grade C, 16.6 ± 10.5 μmol/L), neither of which showed a significant difference.

4. Discussion

Takayanagi reported that carnitine was an amino acid derivative with low molecular weight and played an important role in energy metabolism [7]. He presented the following three reasons for this: a) carnitine is essential for transportation of long-chain fatty acids to mitochondria; b) it adjusts the CoA/acyl-CoA ratio in mitochondria. Replacement of CoA with carnitine generates free CoA in the mitochondria; and c) carnitine removes cytotoxic acyl compounds from the cells as carnitine esters, which are excreted in the urine. Carnitine deficiency is classified into primary and secondary carnitine deficiency [8]. Primary carnitine deficiency is also known as congenital carnitine transporter deficiency or systemic carnitine deficiency. Secondary carnitine deficiency includes other inborn errors of metabolism and acquired medical conditions include: a) decrease in biosyntheses (hepatic cirrhosis, chronic kidney diseases, etc.); b) reduction in intake (long-term management of total parenteral nutrition, malnutrition, etc.); and c) reduction of body stores (pregnant and lactating women, very low birthweight infants, etc.) and those caused by medical interventions (dialysis- or drug-induced).

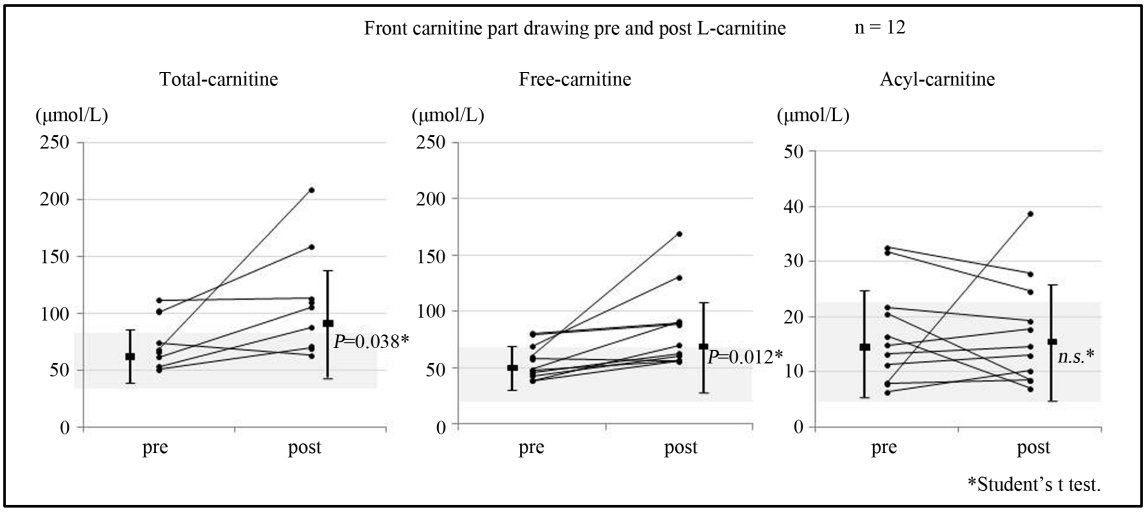

Figure 5. In 12 patients treated with LC, the serum total carnitine levels before and after administrations increased significantly from 71.7 ± 22.8 μmol/L to 101.7 ± 45.5 μmol/L (P = 0.038); free carnitine increased significantly from 54.9 ± 15.4 μmol/L to 84.4 ± 36.2 μmol/L (P = 0.012); and acylcarnitine increased from 16.8 ± 9.1 μmol/L to 17.3 ± 9.8 μmol/L, showing an upward trend.

The cases that we examined in this study were likely to have been those of secondary carnitine deficiency. The symptom of cramps in patients with hepatic cirrhosis is occasionally encountered in clinical practice, and switching therapeutic drugs from BCAA formulations or BCAA granules to oral nutrients for liver failure may improve the symptom [9]. Also, it has been reported that the causes for cramps are mechanism of peripheral neuropathy or myogenic, and decrease in blood taurine levels, which suppress abnormal excitation at the neuromuscular junction. Goto *et al*. discussed that BCAA formulations improved the symptom via decreased levels of free L-tryptophan caused by increased serum albumin levels, followed by facilitated ability to synthesize taurine through correction of amino acid imbalance [10]. We sometimes come across cases in which muscle symptoms occur as a result of carnitine deficiency in dialysis patients as well [11]. In 10 studies by Sakurauchi *et al*., LC formulation was orally administered to 30 maintenance dialysis patients at a dose of 500 mg for 12 weeks, and the patients' somatic symptoms were assessed. As a result, it was reported that muscle symptoms (including fatigue, muscle spasm, and muscle pain) had improved in two-thirds of the patients [12]. In dialysis patients who develop cramps as a result of carnitine deficiency, it is said that muscle symptoms occur due to increased burden on each cell because of insufficient energy production in the muscle cells compared to healthy individuals by shifting of the energy sources from fatty acids to sugars and proteins, which in turn are caused by decreased blood and muscle carnitine levels. It is considered that LC administration allows the long-chain fatty acids to become sufficiently available again, and the acyl compounds accumulated in the cells to be washed out by carnitine, normalizing the cells, and these factors are involved in improvement of the muscle symptoms [13]. A meta-analysis by Lynch *et al*. that integrated the findings of 6 studies revealed that the use of LC significantly improved muscle spasms during dialysis in 2 cases [14]. Changes in the muscle fibers in dialysis patients and carnitine deficiency are also being examined; however, no characteristic changes have been noted [15] [16]. Administration of carnitine to these patients, however, increased the long diameters of type 1 muscle fibers. In these reactions, the type 1 muscle fibers contain many mitochondria, whose metabolism is aerobic. Therefore, what obtains benefits from carnitine administration is type 1 muscle fibers; uptake of fatty acids into the mitochondria increases, cell metabolism increases, the long diameters of the muscle fibers increase, and the proportion of atrophic muscle fibers to total muscle fibers decreases [17]. Although muscle biopsies were not carried out in any of the present cases, such mechanism is likely to be responsible for the improvement in the symptom. We need to consider the doses and duration of administration in future investigations. We also need to search for alternative test items in the future because serum carnitine fractionation is currently not covered by insurance.

References

[1] Malguarnera, M., Vacante, M., Motta, M., *et al*. (2001) Acetly-L-Carnitine Improves Cognitive Functions in Severe

Hepatic Encephalopathy: A Randomized and Controlled Clinical Trial. *Metabolic Brain Disease*, **26**, 281-289, http://dx.doi.org/10.1007/s11011-011-9260-z

[2] Malguarnera, M., Gargante, M.P., Cristaldi, E., *et al*. (2008) Acetyl-L-Carnitine Treatment in Minimal Hepatic Encephalopathy. *Digestive Diseases and Sciences*, **53**, 3018-3025. http://dx.doi.org/10.1007/s10620-008-0238-6

[3] Malguarnera, M., Bella, R., Vacante, M., *et al*. (2011) Acetly-L-Carnitine Reduces Depression and Improves Quality of Life in Patients with Minimal Hepatic Encephalopathy. *Scandinavian Journal of Gastroenterology*, **46**, 750-759. http://dx.doi.org/10.3109/00365521.2011.565067

[4] Moorthy, A.V., Rosenblum, M., Rajaram, R., *et al*. (1983) A Comparison of Plasma and Muscle Carnitine Levels in Patients on Peritoneal or Hemodialysis for Chronic Renal Falure. *American Journal of Nephrology*, **3**, 205-208. http://dx.doi.org/10.1159/000166711

[5] Hiatt, W.R., Koziol, B.J., Shapiro, J.L., *et al*. (1992) Carnitine Metabolism during Exercise in Patients on Chronic Hemodialysis. *Kidney International*, **41**, 1613 -1619. http://dx.doi.org/10.1038/ki.1992.233

[6] Ahmad, S., Robartson, H.T., Golper, T.A., *et al*. (1990) Multicenter Trial of L-Carnitine in Maintenance Hemodialysis Patients 2. Clinical and Biochemical Effects. *Kidney International*, **38**, 912-918. http://dx.doi.org/10.1038/ki.1990.290

[7] Takayanagi, M. (2009) Abnormality. Carnitine Metabolism Child Internal Medicine, **41**, The Special Number 387-389.

[8] Pons, R. and De Vivo, D.C. (1995) Primary and Secondary Carnitine Deficiency Syndrome. *Journal of Child Neurology*, **10**, S8-S24.

[9] Kaneko, Y. and Tsuchiyama, H. (2012) Examination of the Usefulness of the Oral Nutrition Agent for Hepatic Insufficiency to Liver Cirrhosis. *Frontiers in Gastroenterology*, **17**, 94-101.

[10] Goto, N., Iida, K. and Hagisawa, Y. (2001) Usefulness of the Branched-Chain-Amino-Acid Tablet to the Leg Cramps Accompanying Liver Cirrhosis. *Liver*, **42**, 590-599.

[11] Casciani, C.U. and Caruso, U. (1982) Beneficial Effects of L-Carnirine in Post-Dialysis Sundrome. *Current Therapeutic Research*, **l32**, 116-127.

[12] Sakurauchi, Y., Matsumoto, Y., Shinzato, T., *et al*. (1998) Effects of L-Carnitine Supplementation on Muscular Symotpms in Hemodaialyzed Patients. *American Journal of Kidney Diseases*, **32**, 258-264. http://dx.doi.org/10.1053/ajkd.1998.v32.pm9708610

[13] Borum, P.R. and Taggart, E.M. (1986) Carnitine Nutriture of Dialysis Parients. *Journal of the American Dietetic Association*, **86**, 644-647.

[14] Lynch, K.E., Feldman, H.I., Berlin, J.A., *et al*. (2008) Effects of L-Carnitine on Dialysis-Related Hypotension and Muscle Cramps: A Meta-Analysis. *American Journal of Kidney Diseases*, **52**, 962-971. http://dx.doi.org/10.1053/j.ajkd.2008.05.031

[15] Siami, G., Clinton, M.E., Mrak, R., *et al*. (1991) Evaluation of the Effect of Intravenous L-Carnitine Therapy on Function, Structure and Fatty Acid Metabolism of Skeletal Muscle in Patients Receiving Chronic Hemodialysis. *Nephron*, **57**, 306-313. http://dx.doi.org/10.1159/000186280

[16] Ginvenali, P., Fenocchio, D., Montanari, G., *et al*. (1994) Selective Trophic Effect of L-Carnitine Type 1 and 2 Skeletal Muscle Fibers. *Kidney International*, **46**, 1616-1619. http://dx.doi.org/10.1038/ki.1994.460

[17] Takahashi, T., Hashimoto, Y. and Doi, T. (2000) No 2 20 Carnitine and Muscles. *Clinical Dialysis*, **16**, 201-206.