Effects of L-Carnitine Supplementation on Muscular Symptoms in Hemodialyzed Patients

Yasuhiro Sakurauchi, MD, Yoshihiro Matsumoto, MD, Toru Shinzato, MD, Ichiro Takai, MD, Yutaka Nakamura, MD, Motoyoshi Sato, MD, Shigeru Nakai, MD, Masamiki Miwa, MD, Hiroyuki Morita, MD, Toshihiko Miwa, MD, Izumi Amano, MD, and Kenji Maeda, MD

• **Various muscle symptoms are well recognized among patients on maintenance hemodialysis. Carnitine deficiency may be an important factor of dialysis-associated muscle symptoms, whereas high-dose L-carnitine supplementation may result in unphysiologically high plasma levels of carnitine and carnitine esters. We studied the effect of low-dose L-carnitine treatment (500 mg/d) on muscle symptoms, plasma carnitine fractions, and lipid profiles in 30 periodically dialyzed patients with muscular weakness, fatigue, or cramps/aches. After 12 weeks of L-carnitine treatment, about two-thirds of patients had at least some improvement in muscular symptoms, whereas carnitine fractions were normal or slightly above normal ranges, but lipid profiles showed no demonstrable changes. This study also showed the correlation between plasma-free carnitine deficiency and months on dialysis. These results suggest that prolonged low-dose L-carnitine treatment can improve dialysis-associated muscle symptoms by restoring carnitine tissue levels and washing out acyl moieties.**
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INDEX WORDS: L-carnitine supplementation; hemodialysis; muscle symptoms; plasma carnitine levels.

L-CARNITINE (γ-trimethyl-ammonium-β-hydroxybutyrate) is a natural substance whose main physiological role is to transport long-chain fatty acids from the cytoplasm to within the mitochondrial matrix for their β-oxidation in various tissues.[1] The presence of adequate carnitine concentrations in the intracellular compartment is essential for normal fatty acid metabolism in the human organism, which preferentially uses fatty acids for primary energy sources. The skeletal muscle and myocardium display the highest concentrations of L-carnitine,[2] but varied pathological situations deplete the muscle pool of carnitine.

It is commonly known that uremic patients subjected to periodic hemodialysis often become affected by aches, muscle cramps, and muscular exhaustion. These common complaints are rarely helped by effective dialysis and can increase acutely during and after dialysis.[3] Some reports addressing this so-called postdialysis syndrome suggest that perturbation of metabolic balance followed by rapid removal of excessive fluids and urea may lead to muscle cramps and that the loss of useful substances may act on muscle metabolism.

Several studies have shown that hemodialyzed patients exhibit a constant loss of plasma carnitine through filtration and that subsequent endogenous biosynthesis does not sufficiently restore plasma carnitine to basal levels.[4-6] Moreover, Böhmer et al[5] found that the muscle carnitine content after dialysis in hemodialyzed patients was only 10% of that of normal controls. Under such background, some groups have reported beneficial effects of oral supplementation of high-dose L-carnitine (2 g/d) on dialysis-associated muscle symptoms.[3,7] However, a dual response (ie, ketogenic and antiketogenic effects) of L-carnitine supplementation has been elucidated in rats,[8] and low-dose L-carnitine was reported to avoid unphysiological high plasma levels of carnitine and carnitine esters and prevent antiketogenic effects in hemodialysis patients.[9]

The current study was performed to determine whether lower-dose L-carnitine treatment (500 mg/d) is sufficient to alleviate dialysis-associated muscular symptoms and to understand how dosage affects the concentrations of plasma carnitine fractions and lipid profiles in dialyzed patients. In addition, the relation between plasma-free carnitine deficiency and the length of time on hemodialysis therapy in a larger series of maintenance hemodialysis patients was explored.

From the Aichi Clinic, Toyohashi, Japan; the Department of Internal Medicine, Nagoya University Daiko Medical Center, Nagoya, Japan; Johoku Clinic, Nagoya, Japan; the Department of Hemodialysis, Shakaihoken-Chyukyo Hospital, Nagoya, Japan; and Toyohashi Municipal Hospital, Toyohashi, Japan.

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Address reprint requests to Yoshihiro Matsumoto, MD, Department of Internal Medicine, Nagoya University Daiko Medical Center, 1-1-20 Daiko-minami, Higashi-ku, Nagoya 461, Japan. E-mail: matsukun@med.nagoya-u.ac.jp

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MATERIALS AND METHODS

Patients

One hundred seven patients from four participating centers (56 men and 51 women, with a mean age of 59.2 ± 12.9 years) with end-stage renal disease of varying causes were investigated concerning carnitine status. All patients had been stable on hemodialysis thrice weekly (4 hours each dialysis) for 134 ± 88 months and were taking standard medications, including calcitriol, vitamin D_3, calcium carbonate, and erythropoietin. Of the 107 patients, 30 patients (group A; 12 men and 18 women; mean age, 61.9 ± 10.7 years; range, 34 to 78 years; time on dialysis, 138 ± 85 months) were randomly selected to perform the L-carnitine treatment study; they were experiencing obvious muscular symptoms and gave informed consent for our study. We also randomly selected 21 hemodialysis (HD) patients (group B; 9 men and 11 women; mean age, 57.8 ± 10.2 years; range, 26 to 66 years; time on dialysis, 102 ± 70 months) who were completely free of muscular symptoms. HD therapy in both groups was characterized by ultrafiltration control, bicarbonate-base, cellulose, or cellulose acetate membranes. Weight reduction rates in one dialysis session, hematocrit value, and Kt/V, which indicates dialysis volume in group A, were 4.3 ± 2.0%, 30.8 ± 4.0%, and 1.46 ± 0.3, respectively, and those in group B were 4.5 ± 1.7%, 29.4 + 2.7%, and 1.3 ± 0.2, respectively, and there was no significant difference in these parameters between groups. Throughout the carnitine treatment study, drug regimens and diet remained unchanged, and no other coincident conditions were expected to affect muscle function.

Design of L-Carnitine Treatment Study

Before the start of the L-carnitine treatment, 30 patients with muscular symptoms (group A) had blood drawn immediately before and after HD for baseline determination of serum carnitine fraction and lipid profile. The patients were then given a daily dose of 500 mg oral L-carnitine each morning on nondialysis days or after dialysis treatment for 12 weeks. L-carnitine USP (500 mg vanilla flavored chewable wafers) was provided by Vitaline Corporation, Nagoya, Japan. At 2, 4, 8, and 12 weeks after initiation of treatment, each patient was questioned about muscle symptoms (weakness, fatigue, and cramps/aches), and each patient's blood sample was obtained to assess the change in carnitine and lipid profile.

Plasma Carnitine Assay

Plasma carnitine profiles (free carnitine [FC], acyl carnitine [AC], total carnitine [TC]) were determined at Mitsubishi-Kagaku Bio-Clinical Laboratories (Tokyo, Japan), based on the method described by Deufel.[10] Normal values for plasma FC, AC, and TC were 36 to 74 μmol/L, 6 to 23 μmol/L, and 45 to 91 μmol/L, respectively.

Lipid Profile Assay

The plasma lipid profiles were determined after a 12- to 14-hour fast and performed by Special Reference Laboratory (Tokyo, Japan). Total cholesterol, triglycerides, and free fatty acids were assayed by enzymatic methods.[11-13] High-density lipoprotein (HDL) cholesterol was analyzed by selective inhibition methods.[14] Low-density lipoprotein and very-low-density lipoprotein were assayed by heparin calcium precipitation methods.[15,16]

Assessment of Clinical Status

During the study, special attention was given to symptomatology. The 30 patients in group A had been affected by muscular symptoms for at least 2 months. As a control period, we observed the symptoms in each patient for the last 2 weeks before the start of the carnitine treatment. We found no evident change in the symptoms in this period. Each patient was interviewed every four weeks by a physician, who recorded changes in muscle weakness, fatigue, and cramps/aches. A rating score of 0 to 3 was used as follows: 0, no improvement; 1, mild improvement; 2, moderate improvement; 3, marked improvement. The improvement scores were determined by the changes in frequency, severity, site, and duration of the symptoms in each patient. The interviewing physician was the same for the duration of the study.

Statistical Analysis

The results were expressed as means ± SD. Student's *t*-test was used to evaluate statistical significance for two sets of data points. Scheffe's test also was used to analyze statistically more than three data points during treatment. Values of $P < 0.05$ were considered statistically significant.

RESULTS

Relationship Between FC or AC/FC Ratio and Months on Dialysis

To assess the effect of hemodialysis therapy on carnitine deficiency in chronic renal failure patients, the relation between the duration of hemodialysis (months on dialysis) and plasma FC levels in 107 patients on hemodialysis was examined. As shown in Figure 1A, plasma FC decreased gradually in accordance with months on dialysis with a significant correlation. AC/FC ratio was also observed in comparison with months on dialysis, because an AC/FC ratio of greater than 0.25 suggests a free carnitine insufficiency.[17] The AC/FC ratio was shown to increase gradually in accordance with months on dialysis, in contrast with FC levels (Fig 1B). These results indicate that carnitine depletion could be dependent on the duration of dialysis in CRF patients.

Difference of Carnitine Levels Between Patients With Muscle Symptoms and Patients Without Muscle Symptoms

To assess the influence of carnitine depletion on muscle symptoms, we compared plasma FC levels and AC/FC ratio between patients with muscle symptoms (group A) and patients without

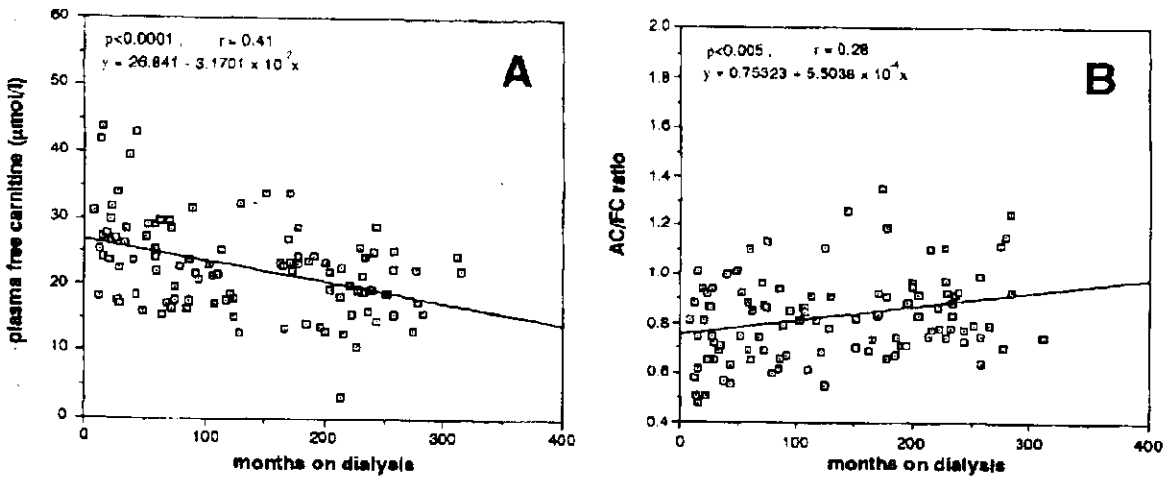

Fig 1. Correlation between the periods for hemodialysis (dialytic age) and free carnitine (FC) (A) or acyl carnitine (AC)/FC ratio (B) in a group of 107 patients on hemodialysis. Plasma samples were taken immediately before hemodialysis. Normal values for FC were 36 to 74 μmol/L.

muscle symptoms (group B). We could exclude the influence of rapid fluid removal and anemia on muscular symptoms, because there was no significant difference of body weight reduction rates in one dialysis session and hematocrit values between group A and group B as described in Materials and Methods. As can be seen in Fig 2, plasma FC levels in group A were significantly lower than those in group B (24.4 ± 8.5 μmol/L *v* 28.2 ± 6.5 μmol/L), and AC/FC ratio in group A was significantly higher than that in group B (0.84 ± 0.19 *v* 0.64 ± 0.17). These results suggest that various muscle symptoms in maintenance hemodialysis patients may be associated with free carnitine deficiency.

Effect of Oral Carnitine Treatment on Dialysis-Associated Symptoms

Thirty patients with muscle weakness, fatigue, or cramps/aches were given L-carnitine (500

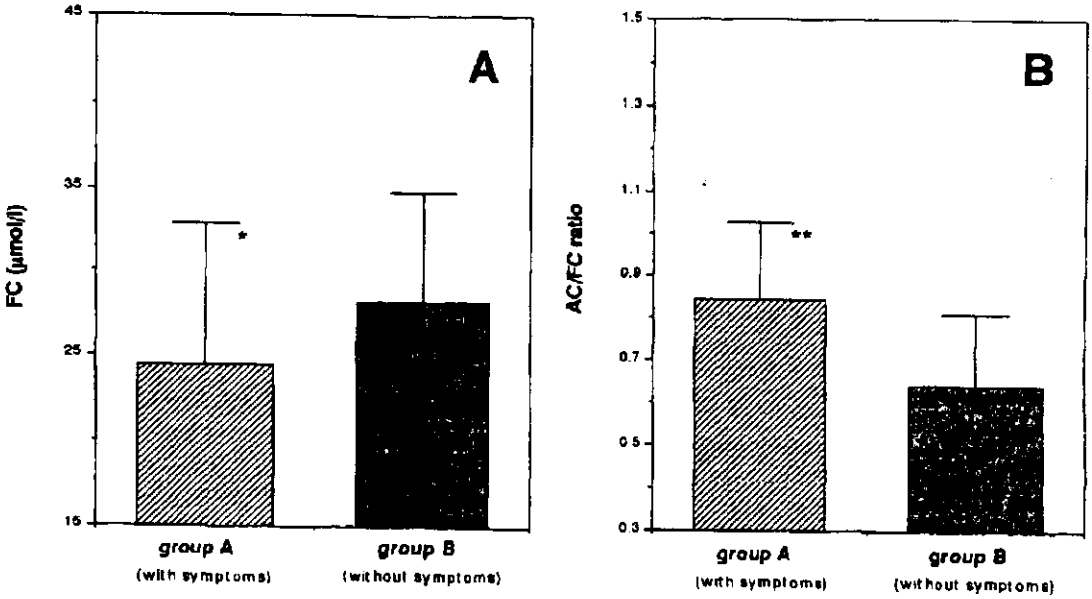

Fig 2. Difference of free carnitine levels (A) and AC/FC ratio (B) between patients with symptoms (group A) and patients without symptoms (group B). This figure shows the means ± SD of data in each group. * denotes $P < 0.05$ for comparison with group B. ** denotes $P < 0.0005$ for comparison with group B. Statistical significance was determined by Student's *t*-test.

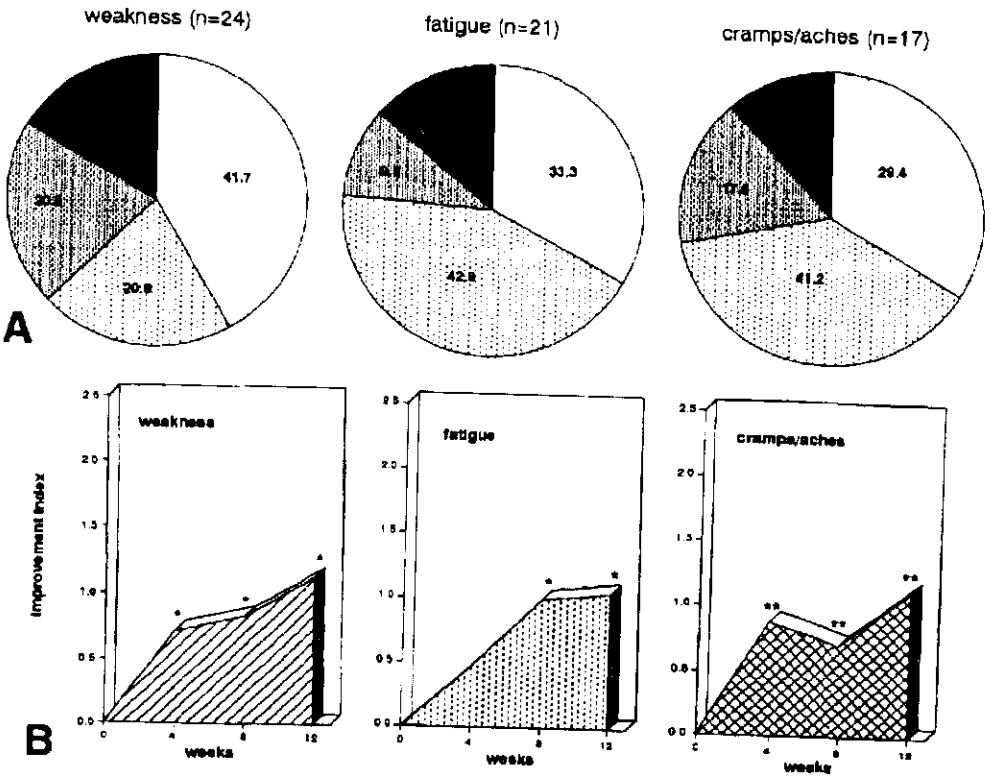

Fig 3. Improvement in dialysis-associated muscle symptoms by oral L-carnitine substitution. (A) Effects on muscle weakness, fatigue, and cramps/aches after 12 weeks of treatment. (B) Improvement index in muscular symptoms during the course of the study. Approximately two-thirds of patients showed some improvement in each symptom. Improvement was scaled as described in Materials and Methods. * denotes $P < 0.005$ for comparison with the baseline; ** denotes $P < 0.05$ for comparison with the baseline. Statistical significance was determined by Scheffe's test. □, None; ▨, mild; ▩, moderate; ■, marked.

mg/d orally) for 12 weeks. During the course of the study, about two-thirds of patients treated with L-carnitine had at least some improvement in muscular symptoms (Fig 3A). This improvement appeared after 4 weeks of L-carnitine therapy and reached mild or moderate improvement as a whole by the end of the study (Fig 3B), consistent with the recent report.[7]

Effect of Oral Carnitine Treatment on Carnitine Fraction Concentration

The mean predialysis values of FC, AC, TC, and AC/FC ratio in the recipient patients are given in Table 1. As shown in Fig 4, the mean FC was lower, TC was borderline, and AC was normal as compared with the normal ranges at the onset of the study. After 4 weeks of L-carnitine treatment, predialysis plasma TC, FC, and AC had increased approximately twofold from each baseline. The FC, AC, and TC levels appeared to reach plateaus after 8 to 12 weeks. Conversely, postdialysis levels of each carnitine fraction were reduced significantly compared with respective predialysis levels, indicating that each fraction was removed easily throughout one dialysis session. Also, predialysis AC/FC ratio, which

Table 1. Predialysis Plasma FC, AC, TC, and AC/FC Ratio During the Course of L-Carnitine Treatment

	Baseline	2 Weeks	4 Weeks	8 Weeks	12 Weeks
Free carnitine (μmol/L)	23.9 ± 8.4	41.2 ± 17.7	55.4 ± 21.4	69.8 ± 38.4	71.8 ± 49.8
Acyl carnitine (μmol/L)	19.3 ± 5.5	28.8 ± 10.1	39.3 ± 13.4	44.3 ± 20.3	43.1 ± 24.7
Total carnitine (μmol/L)	43.2 ± 12.8	69.9 ± 26.6	94.7 ± 33.0	114.1 ± 56.8	114.9 ± 74.0
AC/FC ratio	0.85 ± 0.20	0.73 ± 0.18	0.74 ± 0.18	0.68 ± 0.18	0.64 ± 0.12

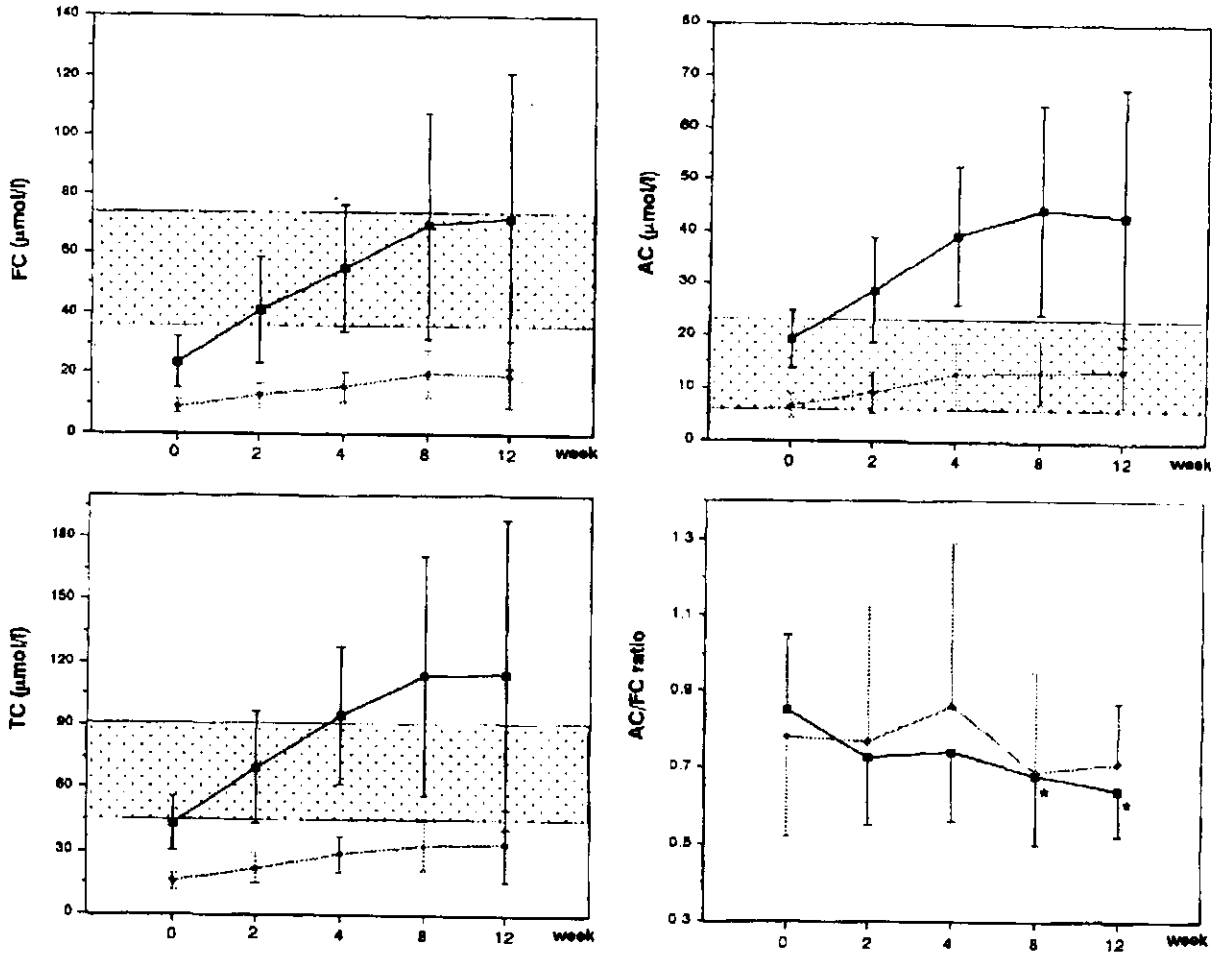

Fig 4. Effects of L-carnitine supplementation on free carnitine (FC), acyl carnitine (AC), total carnitine (TC), and AC/FC ratio. Normal ranges for FC, AC, and TC were indicated by dotted areas. Figure shows means ± SD of each set of patient data. * denotes $P < 0.000005$ for comparison with the baseline. Statistical significance was determined by Scheffe's test. ■, Pre-HD; ⊠, post-HD; ⊡, normal range.

showed significantly elevated levels at baseline, tended to decrease gradually with time toward normalization during the L-carnitine treatment (Fig 4).

Effect of Oral Carnitine Treatment on Plasma Lipid Profiles

The plasma lipid profiles are shown in Fig 5. We compared the values before and after L-carnitine treatment. There were no significant differences in each lipid parameter between at-the-onset and after-12-weeks of L-carnitine treatment.

DISCUSSION

It is now possible to classify carnitine deficiency into two categories. Primary carnitine deficiency is characterized as myopathy and cardiomyopathy associated with lipid accumulation. The acquired forms of carnitine deficiency are observed in patients with cardiac ischemia and chronic hemodialyzed patients. Hemodialysis is of particular note with chronic patients, because it induces a substantial loss of carnitine from the muscular tissue. The typical plasma carnitine profiles in patients on chronic dialysis, as compared with the normal controls, show decreased FC, normal or subnormal TC,[18,19] and significantly elevated AC/FC ratio, corresponding to our current data. This study shows that L-carnitine deficiency progresses with months on dialysis. These results show the importance of L-carnitine supplementation for dialyzed patients, particularly long-term hemodialysis patients.

Previously, Bellinghieri et al[3] showed that

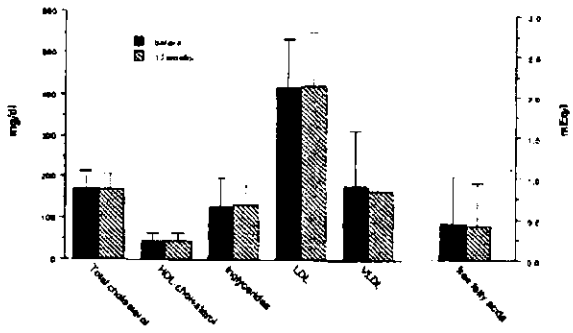

Fig 5. Effects of L-carnitine supplementation on cholesterol, triglycerides, lipoproteins, and free fatty acids in plasma. There were no significant differences between each lipid parameter at the onset (solid column) and after 12 weeks (hatched column) of L-carnitine treatment. Data represent means ± SD. Normal values are as follows: total cholesterol, 150 to 219 mg/dL; HDL-cholesterol, 41 to 86 (male), 41 to 96 (female) mg/dL; triglycerides, 50 to 149 mg/dL; free fatty acids, 0.14 to 0.85 mEq/L.

L-carnitine therapy (2 g/d) can reduce asthenia and cramps while increasing blood and muscle carnitine levels in 14 dialyzed patients. Intravenous L-carnitine trial (20 mg/kg after each dialysis) showed that muscle cramps were reduced only in the carnitine-treated group, whereas improvement in postdialysis asthenia was noticed in both carnitine and placebo groups.[20] Results showed that lower-dose L-carnitine supplementation had beneficial effects in postdialysis syndrome in a larger series of hemodialyzed patients. However, a previous report indicated that oral L-carnitine treatment (2 g/d) had no demonstrable effect in six hemodialysis patients with muscle weakness.[21] The discrepancy between our results and the above report may be attributable to the difference in the duration of dialysis or the number of studied subjects. Alternatively, it might be explained by the difference in the duration or the carnitine doses.[22] Muscle weakness in hemodialysis patients is in fact multifactorial. Poor nutrition combined with the catabolic effect of uremia or hemodialysis may lead to significant weakness. Both myopathy and peripheral neuropathy are common in hemodialysis patients. One postulated cause is the presence of circulating 'middle molecules' that are inadequately removed by commonly used dialysis membranes. Furthermore, renal bone disease such as hyperparathyroidism is known to affect muscle function.[23] Aside from the question of L-carnitine as an essential dietary constituent, the most effective treatment for muscle symptoms is good nutrition. More ministration in diet should therefore be given to hemodialysis patients.

So far, abnormal fatty acid metabolism has been documented in chronic renal failure. In healthy individuals, acyl moieties are conjugated with carnitine, and the resulting acyl carnitine (AC) is excreted in the urine. With impaired renal excretion, short- and long-chain AC accumulates in the plasma. In the current study, L-carnitine treatment promoted increased plasma AC and FC levels. This suggests that the supplemented carnitine continues to conjugate the acyl moieties, and dialyzed patients have an abundant stock (tissue stores) of acyl moieties. Thus, L-carnitine therapy in conjunction with dialysis therapy may act on washing out acyl moieties that may be harmful to cellular metabolism.[24]

Carnitine therapy has not resulted in a similar change in plasma lipids. Some studies have reported a decrease in plasma triglyceride[25,26] and an increase in HDL cholesterol,[27] but some investigators observed no effect or worsening of lipid profile.[28-31] Böhles and Akcetin[8] have shown that the ketogenic effect of carnitine is dose dependent, and maximal oxidative metabolism of fatty acids in the rat was achieved with supplementation of L-carnitine in small amounts (10 mg/kg/d). If large doses of L-carnitine are substituted, significant amounts of acyl moieties may be transported to the cytosol from mitochondria, resulting in the increased synthesis of triglycerides and the reduction of β-oxidation of fatty acids (anti-ketogenic effects). At the completion of this study, mean FC was normal, and mean TC was slightly above normal range—marginally physiological values when compared with some previous reports,[17,32] accounting for no worsening lipid profile with our trial using 500 mg/d of L-carnitine.

In conclusion, the study has shown that plasma free carnitine deficiency is correlated with months on dialysis, and its low-dose supplementation had beneficial effects in postdialysis syndrome with preventing unphysiological high plasma levels of carnitine and negative lipid effects. It is our opinion that prolonged low-dose L-carnitine treatment can improve muscle symptoms of hemodialyzed patients by restoring carnitine tissue levels and washing out cumulative acyl moieties.

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