ARTICLE

Protein, malnutrition and wasting disorders

Efficacy of L-carnitine supplementation for improving lean body mass and physical function in patients on hemodialysis: a randomized controlled trial

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ABSTRACT

Background Carnitine deficiency is common in patients on hemodialysis. However, the efficacy of L-carnitine supplementation for improving lean body mass (LBM) and physical function has not yet been evaluated.
Methods In this multicenter, prospective, parallel, randomized, controlled trial, 91 patients on hemodialysis who developed carnitine deficiency were randomly assigned to receive injections of 1,000 mg L-carnitine 3 times per week after each hemodialysis session (L-carnitine group) or no injections (control group) with monitoring for 12 months.
Results The data for 84 of the 91 patients were available for analysis (L-carnitine group, $n = 42$; control group, $n = 42$). Dry weight and body mass index did not significantly change in the L-carnitine group, but significantly decreased in the control group. Arm muscle area (AMA) did not change significantly in the L-carnitine group but decreased significantly in the control group; the difference in mean AMA between the groups was 6.22% (95% confidence interval [CI] 1.90–10.5; $P = 0.037$). Hand grip strength did not change significantly in the L-carnitine group, but decreased significantly in the control group. The difference in change in hand grip strength between the groups was 4.27% (95% CI 0.42–8.12; $P = 0.030$). Furthermore, LBM did not change significantly in the L-carnitine group but decreased significantly in the control group; the difference in mean LBM between the groups was 2.92 % (95% CI 1.28–4.61; $P = 0.0007$).
Conclusions L-carnitine supplementation is useful in patients who develop carnitine deficiency on hemodialysis because it maintains physical function and LBM.

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Introduction

Carnitine deficiency is known to develop in patients receiving hemodialysis (HD) [1, 2], and may contribute to a number of clinical conditions, including cachexia, erythropoiesis stimulating agent-resistant anemia, myasthenia, insulin resistance, and myopathy, as well as intradialytic symptoms, including muscle cramps, hypotension, and arrhythmias [3, 4].

Sarcopenia is part of an age-related biological phenomenon of diminished reserve and impaired resistance to stressors because of deterioration in several physiological systems. It is characterized by a decline in skeletal muscle mass resulting in decreased muscle strength and decreased physical function [5, 6]. Previous studies have confirmed the association of sarcopenia with adverse health outcomes, including disability, hospital admission, placement in long-term care, reduced quality of life, falls, and mortality [5, 6].

Sarcopenia is also common in patients with chronic kidney disease and is associated with adverse clinical outcomes, especially in individuals with end-stage kidney disease (ESKD) on maintenance dialysis [7–9]. A substantial number of factors affect nutritional and metabolic status in ESKD and have multiple adverse consequences [10]. Physical activity typically decreases with age in both the general population and in patients on maintenance HD [11], and reduced physical function is associated with higher mortality rate in patients on maintenance HD [12].

In spite of the clinical significance of sarcopenia, there are but a few comprehensive intervention programs. Amino acid deficiency, including carnitine deficiency, is thought to be associated with the pathophysiology of this syndrome. However, the effects of L-carnitine on physical function in patients on HD have not been documented. The aim of this study was to determine the effects of L-carnitine treatment for 12 months on the physical and nutritional status of patients undergoing HD.

Subjects and Methods

Patient characteristics

Ninety-one of 146 patients on HD who were screened for eligibility to participate in this multi-center, prospective, randomized, open-label, parallel controlled trial were assigned by random allocation to either an L-carnitine group or a control group. For the L-carnitine group, patients received injections of L-carnitine 1,000 mg (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) 3 times weekly after dialysis sessions for 12 months, while for the control group, patients received standard treatment without L-carnitine injections. An independent investigator with no prior knowledge of the subjects before the start of the trial monitored the order of randomized allocation of patients to the groups. Dynamic balancing randomization was carried out based on duration of HD, age, sex, body mass index (BMI), and presence or absence of diabetes mellitus. In this way, we ensured that baseline characteristics were not significantly different between the groups. The group assignment details were then provided to each of five independent investigators. All participants were treated with HD or hemodiafiltration treatment for 4-h sessions three times per week at any one of three Japanese blood purification centers.

The inclusion criteria were as follows: age ≥20 years and ≤85 years, duration of HD > 12 months at enrollment, carnitine deficiency (free plasma carnitine concentration <40 μmol/L), and patients for whom medical decisions were made at the participating hospitals. The following exclusion criteria were applied: a history of severe cardiac failure,

myocardial infarction, angina pectoris, or stroke within the preceding 6 months; concurrent infectious disease, thyroid disorder, or malignancy; steroid or immunosuppressant therapy; current hospitalization; limb amputation; and L-carnitine treatment within the past 6 months. Participants were regularly provided with dietary guidance by a dietician, particularly those with dietary restrictions on their energy, protein, salt, and fluid intake. Participants were withdrawn from the study, when they developed L-carnitine intolerance during the study period, if medical events occurred leading to death, admission to hospital, substantial disability, or incapacity, or if there was a transfer to another hospital. In the control group, participants were withdrawn from the study when they developed apparent symptoms of L-carnitine deficiency and administration of L-carnitine was to be initiated or when the investigator deemed that withholding L-carnitine treatment would pose a safety problem. The study protocol was approved by the ethics committee of Keiai Hospital and all procedures fully adhered to the Declaration of Helsinki. The study was registered with the University Hospital Medical Information Network (UMIN000025327). All participants provided written informed consent. The study was conducted between January 2016 and December 2017.

Study evaluations

The primary efficacy endpoints were physical function-related parameters, including dry weight, BMI, mid-upper arm muscle area (AMA), hand grip strength, and lean body mass (LBM), which were measured as the magnitude of change from baseline and compared between the two groups. The secondary endpoints were the differences in magnitude of change from baseline in clinical parameters between the two groups.

Blood samples were collected before the beginning of each HD treatment. Serum urea nitrogen and serum albumin levels were measured using routine clinical chemistry methods with commercially available kits. C-reactive protein (CRP) levels were measured using the latex agglutination test. Cardiothoracic ratio was measured on chest radiographs. Normalized protein catabolic rate (nPCR) was calculated for each subject. These variables were assessed at baseline and at the end of the 12-month study period. Efficacy variables were also analyzed within the two groups according to age and diabetes status.

Sarcopenia-related and physical function parameters

All eligible participants were required to undergo dual-energy X-ray absorptiometry (DXA) scans to determine their LBM, fat mass, and skeletal muscle mass. DXA

scanning was performed immediately after the mid-week or end-of-week HD session to minimize any influence of hydration status at the start or end of the study. The DXA scanning was performed using a Lunar iDXA® machine (GE Healthcare, Tokyo, Japan).

Hand grip strength was measured bilaterally in the standing position using a dynamometer adjusted to fit each subject's hand size. The mean of the hand grip strength values in the two hands was used for the analysis. Arm circumference (AC) and triceps skinfold thickness (TSF) were measured by trained instructors. AMA was then calculated using the following formula:[13]

$$AMA(cm^2) = [AC - (\pi)TSF/10]^2/(4\pi).$$

Muscle mass was assessed by performing DXA using height-adjusted skeletal muscle mass with the recommended cutoff values of $7.0\,kg/m^2$ for men and $5.4\,kg/m^2$ for women [14]. Muscle strength was assessed by measuring hand grip strength using the cutoff values of 26 kg for men and 18 kg for women as recommended by the Asian Working Group for Sarcopenia [14]. Thus, sarcopenia was defined as a muscle mass of $<7.0\,kg/m^2$ for men and $<5.4\,kg/m^2$ for women by DXA and hand grip strength of <26 kg for men and <18 kg for women [14]. Hand grip strength (kg/cm^2) was assessed with adjustment for AMA.

Statistical analysis

The data are expressed as the mean ± standard deviation or median (interquartile range) as appropriate. Continuous variables were compared using Mann-Whitney U test or the Student's t-test and categorical variables were compared using Fisher's exact test or chi-square test based on the data distribution. Changes in physical function parameters, including dry weight, BMI, AMA, hand grip strength, and LBM, were defined as the differences between the baseline values and those at the study end; values are shown as the mean and 95% confidence interval (CI). Changes in these parameters between baseline and 12 months between the two groups were analyzed by using logistic regression. Spearman's rank correlation coefficients were used to determine the associations between changes in plasma carnitine concentrations and the variables. Effect size was calculated using Cohen's d. Sample size was calculated based on 80% power, with a presumed effect size of a 2.8% difference in change in LBM from baseline between the groups with a standard deviation of 4.5% according to previous studies [15, 16]. This resulted in a significance level of 0.05 (two-sided) and the estimated number of patients to be evaluated was 84 (42 per group). With an allowed dropout rate of 10% after randomization, we calculated that 90 randomized subjects (45 per group) would

be required. A value of $P < 0.05$ was considered statistically significant. All analysis was carried out using JMP version 12 (SAS Institute Inc., NC, USA).

Results

Study characteristics at baseline

In total, 91 eligible participants were enrolled and randomly assigned the L-carnitine group ($n = 45$) or the control group ($n = 46$); 7 patients had incomplete assessments or did not complete treatment (3 in the L-carnitine group (6.7%) and 4 in the control group (8.7%)). The data for the remaining 42 participants in the L-carnitine group and 42 patients in the control group were entered into the final analysis (Supplementary Figure 1). None of the patients in the control group required initiation of L-carnitine administration. No significant differences were noted in baseline demographic, or anthropometric features, mode of dialysis, type of vascular access, history of cardiovascular disease, or medicines used between the groups (Table 1). The mean plasma free carnitine concentration at baseline was 26.0 ± 6.2 μmol/L in the L-carnitine group and 26.6 ± 6.9 μmol/L in the control group ($P = 0.708$). The prevalence of sarcopenia was 28.6% in the L-carnitine group and 26.2% in the control group ($P = 0.806$).

Effects of L-carnitine supplementation on physical function-related parameters

Table 2 shows the physical function-related and clinical parameters in the two groups at baseline and at the end of the study. There was no significant difference in dry weight between the two groups at baseline. Also, there was no significant change in dry weight in the L-carnitine group (from 57.4 ± 10.9 kg at baseline to 57.7 ± 11.1 kg at the end of the study; $P = 0.419$); however, there was a significant decrease in dry weight in the control group (from 58.4 ± 12.2 kg to 57.8 ± 12.9 kg; $P = 0.035$). The difference in the mean change in dry weight in the L-carnitine group versus the control group at the end of the study was 1.95% (95% CI: −0.36, −0.02; $P = 0.021$; Supplementary Figure 2a). There was no significant change in BMI in the L-carnitine group, but BMI decreased significantly from 21.5 ± 3.8 at baseline to 21.2 ± 3.9 at the end of the study in the control group ($P = 0.044$; Table 2). The difference in the mean change in BMI in the L-carnitine group versus the control group by the end of the study was 2.18% (95% CI: −0.51, −0.07; $P = 0.004$; Supplementary Figure 2b).

There was no significant change in AMA in the L-carnitine group but there was a significant decrease in AMA in the control group from 40.0 ± 10.7 cm^2 at baseline to

Table 1 Patient characteristics at baseline

	L-carnitine group	Control group	P value
n (male %)	42 (71.4)	42 (69.1)	0.811
Age (years)	72 ± 9	72 ± 10	0.712
Duration of dialysis (months)	79 ± 47	74 ± 47	0.669
Diabetes mellitus	20 (47.6)	19 (45.2)	0.829
Alcohol use	7 (16.7)	9 (21.4)	0.584
Smoking	6 (14.3)	4 (11.9)	0.506
Dialysis mode			
Hemodialysis	38 (82.6)	36 (85.7)	0.506
Hemodiafiltration	4 (17.4)	6 (14.3)	0.506
Vascular access			
Arteriovenous fistula	38 (90.5)	37 (88.1)	0.728
Arteriovenous graft	4 (9.5)	4 (9.5)	1.000
Catheter	0 (0)	1 (2.4)	0.314
Comorbidities			
Ischemic heart disease	8 (19.1)	7 (16.7)	0.779
Cerebrovascular disease	3 (7.1)	2 (4.8)	0.649
Peripheral artery disease	1 (2.4)	2 (4.8)	0.562
Medications			
RAS inhibitors	35 (83.3)	32 (76.2)	0.421
Calcium channel blockers	30 (71.4)	31 (73.8)	0.809
β-blockers	11 (26.2)	14 (33.3)	0.480
Vitamin D	37 (88.1)	36 (85.7)	0.749
Phosphate binders	42 (100)	42 (100)	1.000
Statins	21 (50.0)	18 (42.8)	0.517
Iron supplementation	0 (0)	0 (0)	1.000

Values for categorical variables are shown as the percentage or number (percentage) and those for continuous variables as the mean ± standard deviation

RAS renin-angiotensin system

$38.3 \pm 10.7 \, cm^2$ at 12 months ($P = 0.001$; Fig. 1a). The difference in the mean AMA between the groups at the study end was 6.22% (95% CI: 1.90–10.5; $P = 0.037$; Fig. 1b).

Hand grip strength adjusted for AMA showed a significant decrease in the control group from $0.57 \pm 0.25 \, kg/cm^2$ at baseline to $0.55 \pm 0.25 \, kg/cm^2$ at the study end ($P = 0.041$) with no significant change in the L-carnitine group ($0.59 \pm 0.21 \, kg/cm^2$ at baseline, $0.59 \pm 0.21 \, kg/cm^2$ at 12 months; $P = 0.408$; Fig. 2a). The difference in mean change in hand grip strength at 12 months was 4.27% (95% CI 0.42–8.12; $P = 0.030$; Fig. 2b).

There was no significant change in LBM in the L-carnitine group ($44.6 \pm 7.5 \, kg$ at baseline, $44.9 \pm 7.3 \, kg$ at 12 months; $P = 0.224$; Fig. 3); however, there was a significant decrease in LBM in the control group (from $43.3 \pm 9.8 \, kg$ at baseline to $42.5 \pm 9.7 \, kg$ at 12 months; $P = 0.009$). The difference in the mean change in LBM between the groups at 12 months was 2.92 % (95% CI: 1.28–4.61; $P = 0.0007$).

In the L-carnitine group, there was no association between changes in plasma concentrations of free carnitine and the measured variables, including dry weight ($\rho = -0.19$, $P = 0.066$), BMI ($\rho = -0.17$, $P = 0.117$), AMA ($\rho = -0.08$, $P = 0.469$), hand grip strength ($\rho = 0.12$, $P = 0.495$), and LBM ($\rho = -0.13$, $P = 0.224$).

Effects of L-carnitine supplementation on HD efficiency and clinical parameters

There were no significant changes in serum urea nitrogen and nPCR in either of the two groups during study period. Similarly, there was no significant difference in CRP levels or Kt/V between the two groups. Serum albumin level significantly decreased in the control group but not in the L-carnitine group.

Subgroup analysis

The efficacy of L-carnitine was also examined in subgroups of patients according to diabetes status and age (median cutoff 74 years) at baseline. No significant difference was found in sex distribution, age, duration of HD, dry weight, BMI, AMA, hand grip strength, or LBM at baseline between the subgroups with and without diabetes (Table 3). Also, no significant difference was noted in CRP levels between the L-carnitine and the control groups (0.27 [0.08–0.70] mg/dL vs. 0.10 [0.03–0.41] mg/dL; $P = 0.272$). Notably, there were significant differences in percent change in dry weight, BMI, AMA, hand grip strength, and LBM in the subgroup with diabetes but not in the subgroup without diabetes.

When patients were divided according to age (≥74 or <74 years), no significant difference was found in sex distribution, age, duration of HD, dry weight, BMI, AMA, hand grip strength, or LBM at baseline between the two groups (Table 4). However, in the older subgroups, there were significant differences in percent change in dry weight, BMI, AMA, and LBM between the two groups; in the younger subgroups, only the change in LBM was significant between the two groups.

Safety and tolerability

There were no significant adverse events during the study. None of the patients required interruption of treatment and L-carnitine was well tolerated.

Table 2 Changes in clinical and body composition parameters before and after 12 months of treatment with L-carnitine

	L-carnitine group			Control group			Between-group P values	
	Baseline	End	P value	Baseline	End	P value	Baseline	End
Dry weight (kg)	57.4 ± 10.9	57.7 ± 11.1	0.419	58.4 ± 12.2	57.8 ± 12.9	0.035	0.716	0.981
Body mass index (kg/m^2)	21.8 ± 3.5	22.0 ± 3.7	0.089	21.5 ± 3.8	21.2 ± 3.9	0.044	0.711	0.389
Lean body mass (kg)	44.6 ± 7.5	44.9 ± 7.3	0.224	43.3 ± 9.8	42.5 ± 9.7	0.009	0.514	0.208
Fat mass (kg)	13.9 ± 8.0	13.8 ± 8.0	0.731	13.6 ± 6.7	13.8 ± 7.0	0.353	0.832	0.993
Skeletal muscle mass (kg/m^2)	7.2 ± 1.6	7.3 ± 1.6	0.211	7.1 ± 1.6	7.0 ± 1.5	0.001	0.481	0.209
Cardiothoracic ratio (%)	49.2 ± 4.2	49.9 ± 3.8	0.139	50.3 ± 5.3	50.8 ± 5.2	0.411	0.329	0.427
Serum urea nitrogen (mg/dL)	56 ± 14	54 ± 14	0.304	59 ± 12	59 ± 10	0.898	0.382	0.173
Albumin (g/dL)	3.9 ± 0.3	3.8 ± 0.3	0.109	3.8 ± 0.3	3.7 ± 0.3	0.016	0.593	0.573
C-reactive protein (mg/dL)	0.10 [0.04, 0.41]	0.14 [0.06, 0.30]	0.983	0.20 [0.08, 0.69]	0.21 [0.09, 0.71]	0.409	0.253	0.097
nPCR (g/kg/day)	0.82 ± 0.12	0.81 ± 0.12	0.779	0.83 ± 0.13	0.83 ± 0.13	0.804	0.805	0.603
Kt/V	1.35 ± 0.19	1.38 ± 0.16	0.162	1.35 ± 0.17	1.38 ± 0.17	0.101	0.979	0.997

The data are shown as the mean ± standard deviation or median [interquartile range]

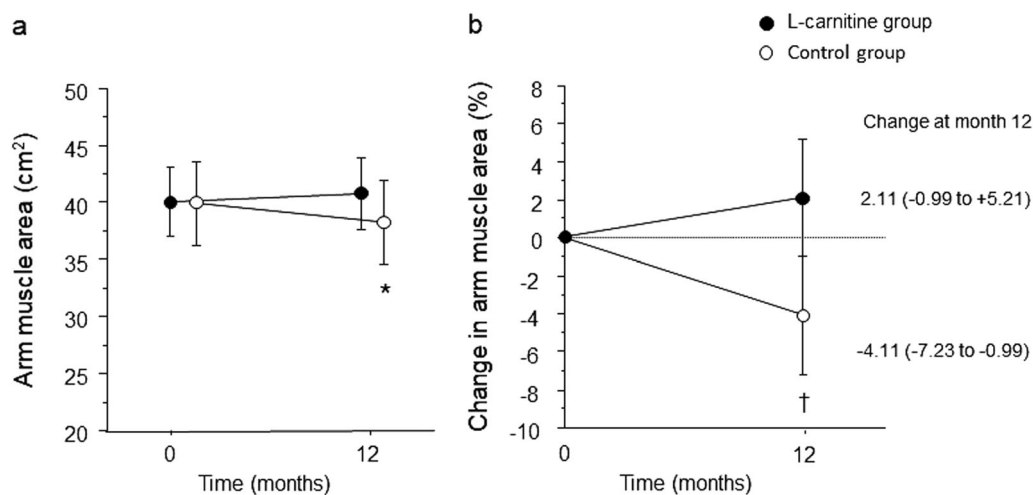*nPCR* normalized protein catabolic rate

Fig. 1 Changes in arm muscle area (AMA) in the L-carnitine and control groups. **a** AMA. **b** Percent change in mean AMA. The data are shown as the mean and 95% confidence interval. Cohen's $d = 0.69$. *$P < 0.01$ vs. baseline. †$P < 0.01$ vs. L-carnitine group

Discussion

In this 12-month study of patients undergoing HD, there was a significant reduction in clinical dry weight, BMI, and serum levels of albumin in the control participants but not in the participants who received L-carnitine supplementation. Furthermore, the percentage mean changes in AMA, hand grip strength, and LBM differed significantly between the two groups, especially in diabetes patients and those who were older. L-carnitine supplementation is reported to have beneficial effects on physical, mental, and cognitive function in older adults [15–17]. Significant increases in lean arm and leg muscle mass without any significant change in arm or leg strength have been reported in healthy older adults receiving carnitine supplementation [18]. To the best of our knowledge, this study is the first to investigate the effect of L-carnitine supplementation on physical status in patients on HD.

Our findings suggest that L-carnitine supplementation has a significant effect on physical status as assessed with AMA, hand grip strength, and LBM. These findings suggest that L-carnitine may have favorable effects on mitochondrial function, including correction of a deficient cellular energy supply, facilitation of long-chain fatty acid transport,
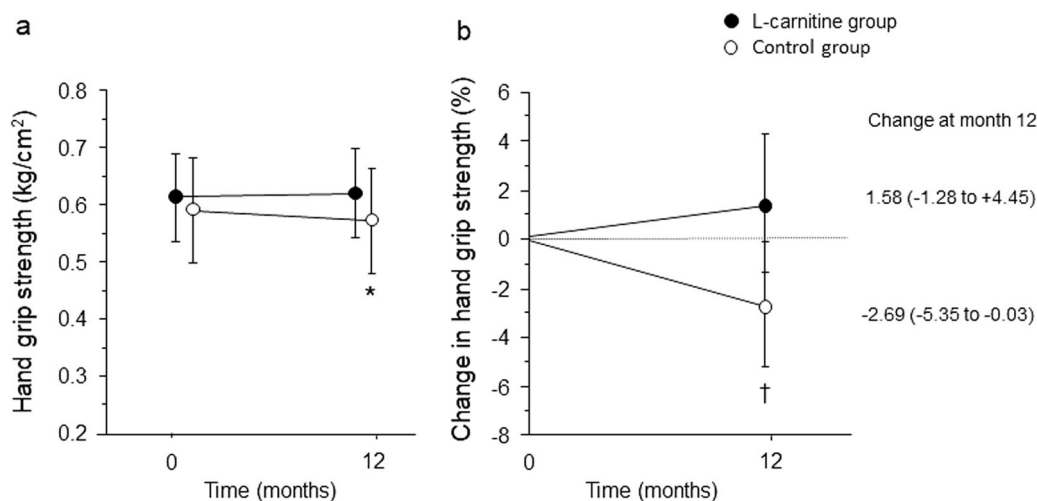
Fig. 2 Changes in hand grip strength adjusted for arm muscle area in the L-carnitine and control groups. **a** Handgrip strength. **b** Percent change in hand grip strength. Data are shown as the mean and 95% confidence interval. Cohen's $d = 0.50$. *$P < 0.05$ vs. baseline. †$P < 0.05$ vs. L-carnitine group
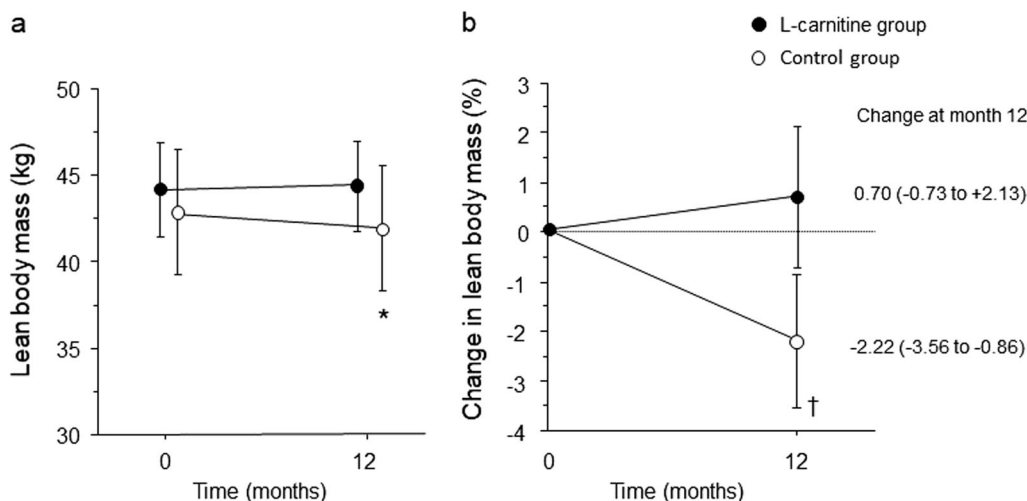

Fig. 3 Changes in lean body mass (LBM) in the L-carnitine and control groups. **a** LBM. **b** Percent change in mean LBM. Data are shown as the mean and 95% confidence interval. Cohen's $d = 0.80$. *$P < 0.01$ vs. baseline. †$P < 0.001$ vs. L-carnitine group

which are the main source of energy in skeletal muscle, into the mitochondria, facilitation of short- and medium-chain fatty acids removal following their accumulation during metabolism, and maintenance of optimal protein and lipid levels [19]. L-carnitine supplementation may result in increased rate of fatty acid oxidation, preservation of muscle glycogen stores, and increased production of ATP [17]. These putative mechanisms may improve and maintain muscle function by improving energy metabolism in skeletal muscle.

The most important risk factors for mortality and morbidity in dialysis patients are inflammation and protein-energy wasting (PEW) [20–22]. The reported prevalence of PEW and frailty in patients on dialysis is ~30%; one third of patients have mild to moderate PEW and about 6–8% of these patients also have severe malnutrition [23–26]. Sarcopenia and its component features are highly correlated with not only hospitalization but also mortality, even after adjustment for well-established risk factors across multiple domains. Some reports have described malnutrition and chronic inflammation in patients on maintenance HD [27, 28]. Also, high levels of proinflammatory cytokines have been shown to cause muscle wasting by stimulating protein catabolism via the ubiquitin-proteasome pathway [29]. In addition, L-carnitine can reduce the production of interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α, all of those are associated with several pathogenic processes [30–32]. In the present study, there was no change in CRP

Table 3 Comparison of patients with and without diabetes between the L-carnitine group and control group

	L-carnitine group	Control group	P value
Diabetes			
n (male %)	20 (60.0)	19 (57.9)	0.893
Age (years)	74 ± 8	71 ± 10	0.427
Duration of HD (months)	52 [42, 83]	51 [45, 74]	0.963
Dry weight			
Baseline (kg)	56.6 ± 11.0	56.7 ± 10.7	0.984
Change (%)	0.9 [0, 2.9]	-0.9 [−2.1, 0]	0.001
Body mass index			
Baseline	21.6 ± 3.5	21.6 ± 3.7	0.978
Change (%)	0.9 [0, 2.1]	−1.1 [−2.2, 1.1]	0.007
AMA			
Baseline (cm^2)	38.3 ± 8.2	39.8 ± 9.7	0.607
Change (%)	2.2 [−0.5, 6.6]	−3.1 [−12.6, 2.1]	0.002
Hand grip strength			
Baseline (kg/cm^2)	0.59 ± 0.21	0.57 ± 0.25	0.645
Change (%)	0.9 [−4.6, 5.5]	−2.5 [−8.1, 3.8]	0.030
Lean body mass			
Baseline (kg)	43.6 ± 8.3	44.6 ± 9.9	0.730
Change (%)	0.5 [−1.6, 3.6]	−1.74 [−4.0, −0.7]	< 0.0001
Non-diabetes			
n (male %)	22 (81.8)	23 (78.3)	0.765
Age (years)	72 ± 8	73 ± 8	0.612
Duration of HD (months)	58 [41,105]	64 [44,77]	0.659
Dry weight			
Baseline (kg)	59.5 ± 8.3	59.5 ± 11.8	0.989
Change (%)	−0.7 [−2.2, 0.8]	−0.4 [−0.9, 0.1]	0.701
Body mass index			
Baseline	22.8 ± 3.6	21.5 ± 3.6	0.231
Change (%)	−0.4 [−1.3, 1.1]	−1.0 [−1.5, 0]	0.305
AMA			
Baseline (cm^2)	41.8 ± 8.4	41.0 ± 10.3	0.801
Change (%)	1.7 [−4.2, 6.5]	−2.8 [−4.9, 1.5]	0.226
Hand grip strength			
Baseline (kg/cm^2)	0.56 ± 0.18	0.57 ± 0.29	0.923
Change (%)	−2.9 [−5.4, 4.0]	−3.1 [−6.8, 4.2]	0.317
Lean body mass			
Baseline (kg)	45.3 ± 6.8	42.2 ± 9.7	0.218
Change (%)	−1.3 [−3.2, 2.8]	−1.2 [−1.9, 0.4]	0.935

The data are shown as the mean ± standard deviation or median [interquartile range]

AMA arm muscle area, *HD* hemodialysis

Table 4 Comparison of older and younger patients between the L-carnitine group and control group

	L-carnitine group	Control group	P-value
Age (years) ≥74			
n (male %)	22 (63.6)	22 (63.6)	1.000
Diabetes (%)	41.0	55.0	0.365
Duration of HD (months)	56 [44, 95]	52 [47, 74]	0.749
Dry weight			
Baseline (kg)	54.9 ± 9.0	52.3 ± 9.7	0.355
Change (%)	0.3 [−0.6, 1.6]	−1.3 [−2.1, -0.7]	0.004
Body mass index			
Baseline	21.7 ± 3.1	20.0 ± 3.3	0.085
Change (%)	0.4 [−0.7, 2.0]	−1.0 [−1.7, −0.6]	0.006
AMA			
Baseline (cm^2)	39.7 ± 8.8	37.9 ± 8.5	0.494
Change (%)	4.1 [0.3, 8.0]	−1.2 [−5.9, 2.7]	0.009
Hand grip strength			
Baseline (kg/cm^2)	0.60 ± 0.14	0.51 ± 0.20	0.066
Change (%)	0.9 [−4.4, 3.0]	−3.3 [−8.3, 3.9]	0.221
Lean body mass			
Baseline (kg)	44.0 ± 8.2	39.3 ± 7.8	0.081
Change (%)	0.16 [−2.1, 2.5]	−1.4 [−2.9, -0.7]	0.019
Age (<74 years)			
n (male %)	22 (80.0)	23 (75.0)	0.705
Diabetes (%)	40.0	40.0	0.525
Duration of HD (months)	53 [41,96]	65 [43,77]	0.879
Dry weight			
Baseline (kg)	61.6 ± 9.4	64.7 ± 9.3	0.302
Change (%)	0.2 [−1.2, 2.1]	0 [−0.9, 0.3]	0.492
Body mass index			
Baseline	22.8 ± 3.9	23.3 ± 3.2	0.715
Change (%)	−0.2 [-1.3, 1.8]	0 [−1.0, 1.3]	0.299
AMA			
Baseline (cm^2)	40.6 ± 8.1	43.3 ± 10.9	0.369
Change (%)	0.4 [−2.9, 4.4]	−4.6 [−12.7, -0.8]	0.077
Hand grip strength			
Baseline (kg/cm^2)	0.57 ± 0.26	0.63 ± 0.28	0.474
Change (%)	1.0 [−4.9, 12.9]	−1.2 [−6.5, 3.4]	0.075
Lean body mass			
Baseline (kg)	45.1 ± 6.7	47.6 ± 9.9	0.346
Change (%)	1.3 [−1.4, 3.8]	−1.9 [−4.7, 1.1]	0.015

The data are shown as the mean ± standard deviation or median [interquartile range]

AMA arm muscle area, *HD* hemodialysis

levels or nPCR, which reflects dietary protein intake. Inflammatory cytokines and lipid peroxides were not evaluated in this study, so further research would be needed to confirm a link between L-carnitine supplementation and reduction in inflammation and prevention of muscle wasting.

Patients with ESKD often develop insulin resistance. Insulin resistance may be caused by malnutrition or sarcopenia. Therefore, inflammation is a common feature in insulin resistance, sarcopenia, and atherosclerosis. Lack of physical fitness might also be a factor in insulin resistance in patients with ESKD [33, 34]. Improvements in tissue oxygenation and exercise tolerance have been shown to reverse insulin resistance in patients with erythropoiesis stimulating agent-resistant anemia [34–36]. L-carnitine has been reported to ameliorate insulin resistance in ESKD patients, by regulating cellular energy metabolism or reducing free fatty acid levels and impaired carnitine metabolism [37–39]. L-carnitine is capable of promoting glucose use in peripheral tissues and cellular insulin sensitivity [40, 41] by

increasing oxidative use of glucose, activating pyruvate dehydrogenase, and decreasing the acetyl-CoA/CoA ratio in the mitochondria [42]. These mechanisms may have led to the preserved physical function seen in our study. However, we could not evaluate the precise changes of insulin resistance or proinflammatory cytokine levels in response to L-carnitine supplementation. Therefore, further study is needed to clarify exactly how L-carnitine effects changes in LBM.

Our study has several limitations. First, it did not include monitoring of markers of oxidative stress or of inflammatory cytokines. Therefore, the mechanisms underlying the preserved physical function mediated by anti-oxidative or anti-inflammatory processes during L-carnitine supplementation remain unknown. Second, it is well known that changes in LBM of <1 kg cannot be measured confidently with DXA; given that we could not measure the tissue hydration, further analysis adjusted for tissue hydration is necessary to assess the changes in LBM. Third, this study was not performed in a double-blind manner. Therefore, an adequately powered, double-blind, randomized clinical trial would be necessary to determine whether improved physical function in patients who receive L-carnitine is associated with better prognosis.

In conclusion, our findings showed the utility of L-carnitine injection for prevention of muscle weakness in patients who develop carnitine deficiency while on HD. The benefits of L-carnitine supplementation in these patients include maintenance of both physical function and LBM. Further large-scale clinical studies would be needed to establish L-carnitine supplementation significantly influences mortality rates for dialysis patients.

Compliance with ethical standards

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