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Effect of L-carnitine on lipid biomarkers of oxidative stress in chronic hemodialysis patients: a randomized controlled trial

Kronik hemodiyaliz hastalarında L-karnitinin oksidatif stresin lipid biyobelirteçleri üzerine etkisi: randomize kontrollü bir çalışma

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ABSTRACT

Objective: This clinical trial aimed to evaluate the effect of L-carnitine on serum levels of lipid biomarkers of oxidative stress in chronic hemodialysis patients.

Methods: From a total of 90 patients with end-stage kidney disease enrolled in this trial, 87 patients completed the study. L-carnitine tablets (250 mg/T) dissolved in 30 mL water (25 mg/kg) were administered orally twice daily before meals for a period of 3 months in the intervention group (n=44). Instead, the controls (n=43) received placebo. Before and 12 weeks after treatment, serum levels of malondialdehyde (MDA), low-density lipoprotein (LDL), and other markers were measured.

Results: The mean serum levels of MDA after hemodialysis (before L-carnitine therapy) were respectively 5.64±2.04 and 5.78±2.12 µmol/L in the intervention and control groups, respectively, which were not statistically different from the levels before hemodialysis (5.60±2.05 and 5.74±2.16 µmol/L, respectively, p>0.05). The reduction in MDA levels after L-carnitine therapy was significantly greater in the intervention group vs. controls (5.17±2.04 vs. 5.60±2.13 µmol/L, p<0.001). In addition, the reduction in LDL levels after treatment was significantly more evident in the intervention group compared with that in the controls (p<0.001). The dose consumption of erythropoietin decreased far more in the intervention group (from; 8000±520 to 3750±418 unite/week) than in the control group (from; 8000±318 to 6000±528) after 5 months of follow-up (p=0.029).

Conclusion: Oral administration of L-carnitine in chronic hemodialysis patients may remarkably modulate lipid marker levels of oxidative stress and reduce the dose consumption of erythropoietin without any side effects.

Keywords: L-carnitine, Malondialdehyde, low-density lipoprotein, end-stage kidney disease, hemodialysis

ÖZ

Amaç: Bu klinik çalışma, kronik hemodiyaliz hastalarında L-karnitinin oksidatif stresin lipid biyobelirteçlerinin serum seviyeleri üzerindeki etkisini değerlendirmeyi amaçladı.

Yöntemler: Bu çalışmaya katılan son dönem böbrek hastalığı olan toplam 90 hastadan 87'si çalışmayı tamamladı. Müdahale grubuna (n=44) 30 mL su (25 mg/kg) içinde çözülmüş L-karnitin tabletleri (250 mg/T) 3 ay süreyle yemeklerden önce günde iki kez oral olarak uygulandı. Bunun yerine kontrollere (n=43) plasebo verildi. Tedaviden önce ve tedaviden 12 hafta sonra malondialdehit (MDA), düşük yoğunluklu lipoprotein (LDL) ve diğer belirteçlerin serum seviyeleri ölçüldü.

Bulgular: Hemodiyaliz sonrası (L-karnitin tedavisi öncesi) ortalama serum MDA düzeyleri müdahale ve kontrol gruplarında sırasıyla; 5,64±2,04 ve 5,78±2,12 µmol/L olarak belirlendi, hemodiyaliz öncesi düzeylerden istatistiksel olarak farklı değildi (sırasıyla; 5,60±2,05 ve 5,74±2,16 µmol/L, p>0,05). L-karnitin tedavisinden sonra MDA düzeylerindeki azalma, kontrollere kıyasla müdahale grubunda anlamlı derecede daha fazlaydı (5,17±2,04'e karşı 5,60±2,13 µmol/L, p<0,001). Ayrıca tedavi sonrasında LDL düzeylerindeki azalma, kontrollere kıyasla müdahale grubunda anlamlı düzeyde daha belirgindi (p<0,001). Eritropoietin doz tüketimi müdahale grubunda (8000±520 unite/haftadan 3750±418 unite/haftaya) kontrol grubuna göre (8000±318 unite/haftadan 6000±528 unite/haftaya) 5 aylık takip sonrasında çok daha fazla azaldı (p=0,029).

Sonuç: Kronik hemodiyaliz hastalarında L-karnitinin oral yoldan uygulanması, oksidatif stresin lipid belirteç düzeylerini önemli ölçüde modüle edebilir ve herhangi bir yan etki olmaksızın eritropoietinin doz tüketimini azaltabilir.

Anahtar Sözcükler: L-karnitin, malondialdehid, düşük yoğunluklu lipoprotein, son dönem böbrek hastalığı, hemodiyaliz

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INTRODUCTION

The incidence and prevalence of chronic kidney disease (CKD) is increasing worldwide (1). Despite progress in treatment and increasing survival rates, atherosclerosis and cardiovascular disease are still the most important causes of mortality among patients with end-stage renal disease (ESRD) (2,3). The progression of dyslipidemia in these patients is affected by several factors, including carnitine deficiency, which can lead to lipid metabolism disorders (4,5). Carnitine or trimethyl aminobutyric acid is a natural and vitamin-like substance in the human body that participates in many metabolic processes such as ketogenesis regulation, control of mitochondrial energy release, and transfer of long-chain fatty acids from the cytoplasm to mitochondria. Therefore, the presence of sufficient amounts of carnitine in cells is essential for the normal oxidation of fatty acids, especially in tissues such as the heart and muscle, which are dependent on fatty acids to generate energy (6). Plasma levels of L-carnitine in chronic hemodialysis patients are reduced due to abnormal kidney and liver synthesis and its loss through the dialysis membrane, whereas lipid factors of oxidative stress, such as malondialdehyde (MDA), remain high (7,8). Oxidation of fatty acids and lipid metabolism are heavily influenced by carnitine deficiency (9). Inappropriate metabolism of fatty acids occurs along with an increase in free radical production (oxidative stress), insulin resistance, and cell apoptosis Schreiber (10). MDA is a lipid biomarker produced by lipid oxidation, and its level increases under conditions of increased oxidative stress (9).

So far, few studies have been conducted to evaluate the effect of L-carnitine on the level of lipid biomarkers of oxidative stress. Therefore, our study aimed to investigate the effect of this drug on the levels of lipid biomarkers of oxidative stress, i.e., MDA and low-density lipoprotein (LDL), in chronic hemodialysis patients. The L-carnitine dosage used in this study was less than that used in previous studies. Therefore, if its lower doses are effective, it will definitely be more cost-effective overall.

MATERIALS AND METHODS

Trial Design

This controlled double-blind randomized clinical trial was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (approval number: IR.AJUMS.REC.1394.79 and IRCT2015112224645N2). Eligible patients with end-stage renal failure and chronic hemodialysis who were referred to the hemodialysis departments of Ahvaz hospitals were enrolled in this study.

Case Study Selection Criteria

Inclusion criteria included hemodialysis patients older than 18 years who were dialyzed three times a week and who had a history of hemodialysis for at least 3 months. The exclusion criteria included patients who had:

1. An acute illness at least one month before starting the study.
2. Any allergies to L-carnitine.
3. Liver cirrhosis (aspartate aminotransferase, alanine aminotransferase >45 IU/L).
4. Heart failure (ejection fraction <35%).

Also, patients who are taking vitamin E, C, or any antioxidant

Compliance with Ethical Standards

All procedures performed in this clinical trial involving human participants were in accordance with the ethical standards of the national research committee and with the 2008 Helsinki Declaration and its later amendments or comparable ethical standards. This clinical trial was approved by the Regional Research Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethical Code: IR.AJUMS.REC.1394.79).

Randomization, Blinding, and Allocation Concealment

Considering the main purpose of the research, the researcher's idea, and previous studies (11), the sample size was calculated using the following formula ($\beta=0.8$, $\alpha=0.05$):

$$n = \frac{(z_{1-\alpha/2} + z_{\beta})^2 [p_1(1-p_1) + p_2(1-p_2)]}{(p_1 - p_2)^2}$$

In total, 103 patients were assessed for eligibility. Thirteen patients were excluded from the trial due to not meeting inclusion criteria or refused to participate in the study (Figure 1). Eventually, 90 eligible patients were randomly divided into two parallel groups, including patients under prescribed drug ($n=44$) and patients under prescribed placebo ($n=43$). To maintain single-blinding, we used a "simple randomization" by randomly assigning patients to the intervention and control groups using a 6-item randomized block method and an equal allocation ratio (1:1) (12). During the study, the physician, patients, and the main investigator were blinded to drug allocation.

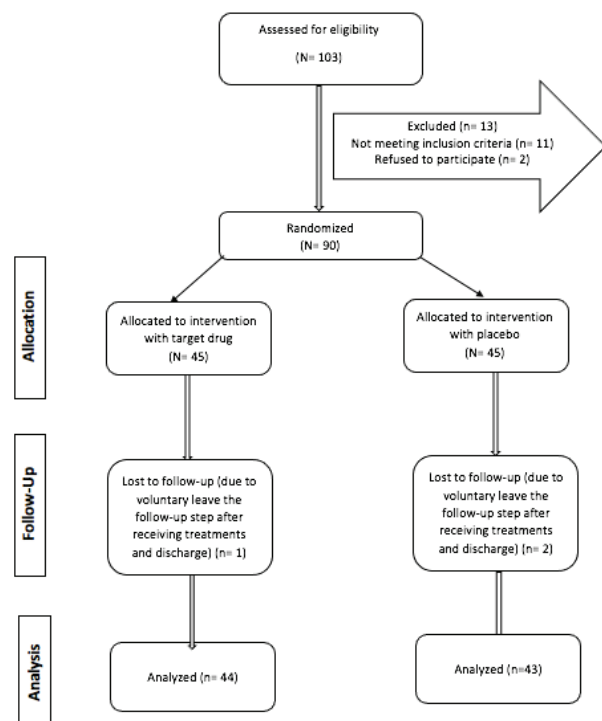


Figure 1. Patient flow diagram.

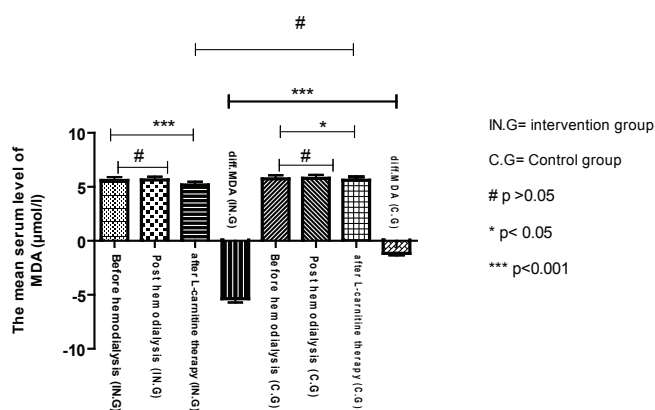


Figure 2. Comparison of malondialdehyde levels between the intervention group (L-carnitine tablets) and controls (placebo) before and after L-carnitine therapy.

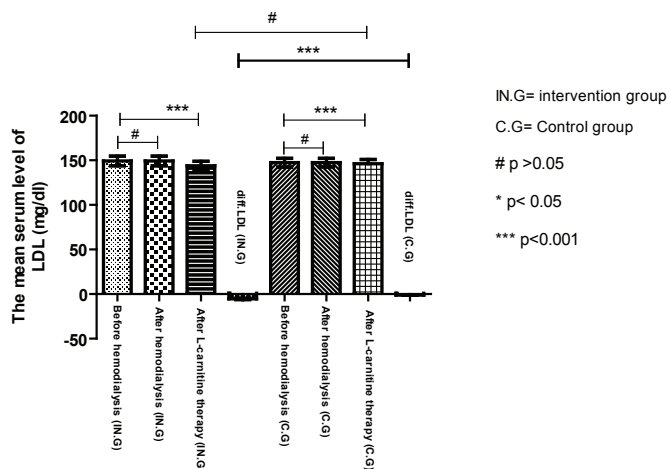


Figure 3. Comparison of low-density lipoprotein levels between the intervention group (L-carnitine tablets) and controls (placebo) before and after L-carnitine therapy.

Drug and Placebo Test

L-carnitine tablets (Behdadaru Afarinesh Company; Isfahan Scientific and Research Township; IRAN): L-carnitine tablets (250 mg per tablet, 250 mg/T) dissolved in 30 mL water (25 mg/kg) were administered orally twice daily before meals for three months for the intervention group. Instead, the controls received a placebo (similar to L-carnitine) dissolved in 30 mL water.

The placebo capsules were prepared at the pharmaceutical laboratory of Ahvaz Jundishapur University of Medical Sciences using a capsule filling machine approximately 2 weeks before administration and were then stored in the same bottles as L-carnitine bottles. The placebo capsules were completely the same as the L-carnitine tablets in terms of size, color, and appearance, as the recognition of the slight difference in their weight was difficult by visual observation (whether before or after dissolving in 30 mL water). Its compounds were microcrystalline cellulose, lactose, corn starch, sorbitol, and talc (2% of total tablet weight), and its

taste after dissolution in water was the same as that of dissolved L-carnitine tablets.

Monitoring Interventions, Recording, and Ensuring Compliance

Before any intervention, sufficient information and the advantages of the intervention were explained to all patients, and their voluntary consent form and readiness for cooperation were received. All information about the supplement usage prescribed on the bottles (two capsules 250 mg, daily before meals, for 12 weeks) for them.

A booklet was provided to each patient, including a schedule of supplement consumption. Moreover, to ensure compliance, our colleagues tried to call each participant daily to remind them of the number and time of supplement consumption as well as to evaluate the probability of side effects. After 3 months of daily follow-up, the bottles were collected, and the remaining capsules were calculated and recorded in the data tables.

Clinical Laboratory Testing

Before and 12 weeks after L-carnitine therapy, serum levels of MDA ($\mu\text{mol/L}$), LDL (mg/dL) were measured using standard thiobarbituric acid and calorimetric methods.

Renal blood flow [cortical (CBF) and medullary (MBF) (mL/min/100 g)] was evaluated by conventional high-contrast magnetic resonance imaging, as previously described by Dujardin et al.'s (13) study. The serum levels of CKD-associated biomarkers [CRP (mg/dL), hemoglobin (mg/dL), albumin (g/dL), creatinine (mg/dL), PTH (pg/mL), ferritin (ng/mL), potassium (mEq/L), blood urea nitrogen (mg/dL), calcium (mg/dL), and phosphorus (mg/dL)] were measured by ELISA and electrochemical coulometry, respectively.

Statistical Analysis

All data were analyzed using SPSS version 26. The data related to qualitative and quantitative variables were reported as frequency or percentage and mean \pm standard deviation, respectively. Based on the results of the Kolmogorov-Smirnov test, all data were analyzed and compared with each other by different tests, including Mann-Whitney U, chi-square, independent t-test, and paired t-test. However, some parameters were merely evaluated to confirm the patients with CKD and were not compared. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Data

From a total of 90 patients, three patients were excluded from the study because of voluntary leave at the follow-up step after receiving treatments and discharge (one from the intervention arm and two cases from the control arm). Eventually, 87 patients completed this clinical trial (44 cases in the intervention group and 43 cases into the control group). In total, 44 (50.57%) and 43 (49.43%) were male and female, respectively. The mean age (years) of the intervention and control groups were respectively 50.27 ± 9.92 and 49.04 ± 9.61 years, respectively. There were no statistically significant differences in age and gender between the two studied groups ($p > 0.05$; Table 1). In addition, there were no statistically significant differences between

the two groups in terms of duration of dialysis (years), the primary cause of chronic renal failure, and ultrafiltration rate ($p>0.05$; Table 1).

Laboratory Changes

Before starting the new hemodialysis, the mean serum level of MDA was respectively 5.60 ± 2.05 and 5.74 ± 2.16 $\mu\text{mol/L}$, respectively, among the intervention and control groups. The serum levels of MDA after the hemodialysis process and before L-carnitine therapy were respectively 5.64 ± 2.04 $\mu\text{mol/L}$ and 5.78 ± 2.12 $\mu\text{mol/L}$, respectively, in the intervention and control groups, which were not statistically different from the levels before hemodialysis according to a paired

Table 1. Demographic characteristics of chronic hemodialysis patients

Variables	Intervention group, (n=44)	Control group, (n=43)	PV (1)
Gender (sex)			
Male	23 (52.27%)	21 (48.84%)	0.83
Female	21 (47.73%)	22 (51.16%)	
Age (years)	50.27 ± 9.92	49.04 ± 9.61	0.80
Duration of dialysis (years) in all patients: Under 3 years			
3-6	18 (40.91%)	20 (46.50%)	0.67
Over 6 years	16 (36.36%)	19 (44.20%)	0.51
Over 6 years	10 (22.73%)	4 (9.30%)	0.14
Primary causes of chronic renal failure in all patients:			
Hypertension	15 (34.10%)	13 (30.23%)	0.82
Diabetes mellitus	11 (25%)	12 (27.91%)	0.81
Glomerulonephritis	6 (13.64%)	7 (16.28%)	0.77
Polycystic kidney disease	3 (6.82%)	4 (9.30%)	0.71
Renal stone	2 (4.54%)	2 (4.65%)	1
Infection	2 (4.54%)	2 (4.65%)	1
Unknown	5 (11.36%)	3 (6.98%)	0.71
Kt/V	1.42 ± 0.05	1.42	
Albumin (g/dL)	3.39 ± 0.07	3.40 ± 0.10	
Creatinine (mg/dL)	6.88 ± 0.10	6.86 ± 0.20	
PTH (pg/mL)	402.06 ± 12.07	402 ± 17	
Ferritin (ng/mL)	387.7 ± 16.17	389 ± 12.08	$p>0.05$
Potassium (mEq/L)	4.22 ± 0.02	4.25	
BUN* (mg/dL)	56.70 ± 8.40	57 ± 7.90	
Calcium (md/d)	8.39 ± 0.50	8.42 ± 0.20	
Phosphorus (mg/dL)	4.92 ± 0.05	4.94 ± 0.08	
UFR* (cc/kg/h):			
>10	34 (77.27%)	30 (69.77%)	0.98
10-13	7 (15.90%)	11 (25.58%)	
>13	3 (6.82%)	2 (4.65%)	

*BUN: Blood urea nitrogen, *UFR: Ultrafiltration rate.

t-test ($p>0.05$). The mean serum level of MDA after L-carnitine therapy (post-hemodialysis) was 5.17 ± 2.04 $\mu\text{mol/L}$, which was statistically lower than its baseline levels ($p<0.001$). Although MDA levels significantly decreased in the controls, the mean difference in reduction of MDA levels pre- and post-treatment was significantly greater for the intervention group ($p<0.001$). Based on the outgroup analysis, there were no statistically significant differences in the base levels of MDA, whether before or after hemodialysis, between the two groups ($p>0.05$; Table 2).

Although there were no statistically significant differences in the base level of LDL between the two groups ($p>0.05$; Table 2), the reduction in LDL level after treatment was significantly greater in the intervention group than in the control group ($p<0.001$).

Although the serum levels of hemoglobin after L-carnitine therapy [11.75 (9-12.50) mg/dL] were significantly higher than those before L-carnitine therapy [11.55 (9.02-12.45); $p<0.001$], the increased mean level did not significantly differ from the mean level in the control group ($p=0.33$; Table 2).

The level of CRP after L-carnitine therapy [7.50 (5.62-8.90) mg/dL] significantly decreased compared with its level before L-carnitine therapy (post-hemodialysis) [9 (7.72-11.87), $p<0.001$], yet its decreased mean level was not significantly different from its decreased mean level in the control group ($p=0.12$; Table 2).

Evaluation of the levels of renal blood flow [cortical and medullary (mL/min/100 g)] before and after L-carnitine therapy did not show any statistically significant difference between the two groups ($p>0.05$; Table 2). However, the levels of CBF and MBF were not significantly increased after L-carnitine therapy. Moreover, based on the intra- and outgroup analyses, the levels of systolic and diastolic blood pressure (systolic BP= 129.41 ± 4.50 , diastolic BP= 80.77 ± 7.87) after L-carnitine therapy were not significantly different from their levels before L-carnitine therapy (systolic BP= 129.57 ± 4.82 , diastolic BP= 81.02 ± 8.18); $p>0.05$) compared with the control group (Table 2).

Efficacy and Safety

The dose consumption of erythropoietin was $8,000\pm 520$ and $8,000\pm 318$ (unite/week) for the intervention and control groups, respectively; its dose was far more decreased in the intervention group ($3,750\pm 418$) than in the control group ($6,000\pm 528$) after 5 months of follow-up ($p=0.029$). L-carnitine therapy had no side effects on the patients.

DISCUSSION

Hyperlipidemia and anemia are important dialysis-related complications in patients with CKD under chronic hemodialysis (14). A cause of these complications is a reduction in serum L-carnitine levels. Carnitine is effective in transferring long-chain fatty acids into the mitochondria and stabilizing the erythrocyte membrane (15,16). The low serum concentration of carnitine in hemodialysis patients is due to several reasons, including 1) the drainage and withdrawal of carnitine from the dialysis filtrate membrane cause a decrease in its plasma concentration by approximately 70 to 75% (17); 2) given that the kidney is one of the main sites for carnitine synthesis, renal damage can lead to disruption in carnitine synthesis (17); 3) The amount of carnitine received from the diet in hemodialysis patients may be less than the required amount (17,18).

Table 2. Laboratory changes before and after L-carnitine therapy compared with the control group

Variables	Intervention group, (n=4)	Control group, (n=43)	PV (1)
Hemoglobin levels (mg/dL):			
-before L-carnitine therapy (post-hemodialysis)	11.55 (9.02-12.45)	11.80 (9.80-12.80)	0.40
after L-carnitine therapy	11.75 (9-12.50)	12 (10-12.70)	0.66
Mean (SD) difference	0.17 (0.20)	0.16 (0.27)	0.33
PV (2)^{WSR}	<0.001***	<0.001***	
LDL levels (mg/dL): before hemodialysis			
-before L-carnitine therapy (post-hemodialysis)	149.27±17.92	147.32±15.73	0.60
after L-carnitine therapy	149.34±17.74	147.40±15.62	0.58
after L-carnitine therapy	143.90±16.35	146.16±15.57	0.51
Mean (SD) difference	-5.36 (2.27)	-1.16 (0.81)	<0.001***
PV (2)	<0.001***	<0.001***	
CRP (mg/dL):			
-before L-carnitine therapy (post-hemodialysis)	9 (7.72-11.87)	9.50 (8-13.50)	0.55
after L-carnitine therapy	7.50 (5.62-8.90)	7 (5.50-9.50)	0.95
Mean (SD) difference	-2.85 (2.90)	-3.89 (4.88)	0.12
PV (2)	<0.001***	<0.001***	
MDA (μmol/L) in the intervention group:			
-MDA (μmol/L) before hemodialysis	5.60±2.05	5.74±2.16	0.71
-MDA before L-carnitine therapy (post-hemodialysis)	5.64±2.04	5.78±2.12	0.74
-MDA after L-carnitine therapy	5.17±2.04	5.60±2.13	0.33
Mean (SD) difference	-0.42 (0.24)	-0.14 (0.35)	
PV (2)	<0.001***	0.01*	<0.001***
Renal blood flow in the intervention group			
- Cortical blood flow (ml/min/100g) before L-carnitine therapy	102.88±7.27	105.14±2.67	0.06
- Cortical blood flow (ml/min/100g) after L-carnitine therapy	103.22±7.16	105.23±2.57	0.08
Mean (SD) difference	0.34 (1.14)	0.09 (0.30)	0.17
PV (2)^{WSR}	0.053	0.07	
- Medullary blood flow (mL/min/100 g) before L-carnitine therapy	19.27±3.57	18.97±3.84	0.71
- Medullary blood flow (mL/min/100 g) after L-carnitine therapy	19.38±3.54	19.04±3.94	0.67
Mean (SD) difference	0.11 (0.38)	0.07 (0.25)	0.53
PV (2)^{WSR}	0.057	0.08	
Systolic BP:			
-Systolic BP* (mmHg) before L-carnitine therapy	129.57±4.82	129.74±4.40	0.86
-Systolic BP* (mmHg) after L-carnitine therapy	129.41±4.50	129.60±4.20	0.83
Mean (SD) difference	-0.16 (0.64)	-0.14 (0.46)	0.87
PV (2)	0.10	0.06	
Diastolic BP in the intervention group:			
-Diastolic BP* (mmHg) before L-carnitine therapy	81.02±8.18	80.83±8.25	0.86
-Diastolic BP* (mmHg) after L-carnitine therapy	80.77±7.87	80.69±8.05	0.83
Mean (SD) difference	-0.25 (0.61)	-0.14 (0.56)	0.87
PV (2)	0.88	0.10	

PV (1): Comparing the mean levels of biomarkers between two groups based on the Mann-Whitney test and/or an independent samples t- test. PV (2): Comparing the mean levels of biomarkers in each group at baseline and after L-carnitine therapy based on the Wilcoxon signed rank test and/or a Paired t-test. Mean (SD) difference between pre- and post-treatment. * BP: Blood pressure, MWU: Mann-Whitney U test, WSR: Wilcoxon signed-rank test.

Fatouros et al. (19) examined the effects of L-carnitine on oxidative stress in hemodialysis patients. In their study, 40 hemodialysis patients were selected. They treated the control group with intravenous L-carnitine (20 mg/kg for 8 weeks and 3 times per week) after each dialysis. The levels of lactate, MDA, glutathione, and carboxylase protein were measured before beginning the study. At the end of the study, the aforementioned indices were again measured. There was a significant reduction in the levels of oxidative stress markers (19). Our findings confirm the results of Fatouros et al.'s (19) study in which L-carnitine therapy significantly decreased the mean levels of lipid biomarkers of oxidative stress (MDA and LDL) in chronic hemodialysis patients; however, we used oral L-carnitine.

In 2010, Safari et al. (20) studied the effect of carnitine on MDA in 27 hemodialysis patients. Their results showed that oxidative stress worsens during hemodialysis. In Safari et al. (20) study, 55.60% of patients had L-carnitine deficiency. The mean values of pre-hemodialysis MDA and L-carnitine were 4.17 ± 1.24 $\mu\text{mol/L}$ and 7.67 ± 3.60 mg/L, respectively, while those following hemodialysis were 4.98 ± 1.20 $\mu\text{mol/L}$ and 2.07 ± 1.60 mg/L, respectively. Finally, there was found a significant relationship between carnitine reduction and MDA increase before and after hemodialysis (20). In this regard, our findings are in accordance with their results in which the hemodialysis process led to a worse change in the levels of oxidative stress-related lipid markers (i.e., MDA and LDL), but not significantly so ($p > 0.05$). However, we did not measure serum carnitine levels pre- and post-treatment and merely focused on the effects of L-carnitine therapy on various biomarkers. In our study, the baseline value of pre-hemodialysis MDA was partially higher than that in Safari et al. (20) study; this is probably because our patients had previously experienced hemodialysis-related oxidative stress. Furthermore, in our trial, a significant descending change in the levels of MDA and LDL following L-carnitine therapy was indicative of the remarkable role of L-carnitine in reducing the effect of hemodialysis-related oxidative stress on lipid peroxidation.

Naini et al. (21) also described the effect of this drug on the level of lipid biomarkers. L-carnitine causes a significant reduction in triglyceride and a significant increase in HDL levels, but not significantly change in LDL. In addition, a decrease in total cholesterol was not significant in the carnitine group (21). Although our research did not address HDL, our results indicate a significant change in the levels of LDL and MDA following L-carnitine therapy.

Furthermore, our findings showed no significant changes in the levels of CBF and MBF after L-carnitine therapy. In addition, the levels of systolic and diastolic blood pressure after L-carnitine therapy did not considerably differ from their levels before L-carnitine therapy, which confirmed the findings of Kudoh et al. (22). However, Kudoh et al. (22) reported that systolic and diastolic blood pressures were insignificantly increased after 3 months of L-carnitine therapy; such a questionable increase is contrary to our findings.

In this study, there was a significant inverse correlation coefficient between MDA levels and medullary and cortical blood flow ($r > 0.50$, $p < 0.001$), whether before or after L-carnitine therapy. Such a correlation may indicate the effect of MDA-related oxidative stress on vasoconstriction and renal blood flow. In this study, L-carnitine therapy modulated the adverse effect of MDA-related oxidative stress on renal blood flow, but not significantly.

Furthermore, the remarkable impact of L-carnitine therapy on reducing the dose consumption of erythropoietin after 5 months indicates its strong therapeutic role in chronic hemodialysis patients.

Study Limitations

The exact information about the patient's diet and the possible stressful conditions was beyond our control, which may have affected the laboratory results. Serum carnitine levels were not measured among patients; therefore, this study has not assessed its changes and/or correlations with other biomarkers.

Study Strength

In this randomized and single-blinded clinical trial, the impact of L-carnitine therapy on renal blood flow, blood pressure, and the dose consumption of erythropoietin was evaluated in addition to lipid and hematologic markers.

CONCLUSION

Our findings suggest that oral administration of L-carnitine in patients with ESRD undergoing chronic hemodialysis has a significant effect on modulating the lipid biomarkers of oxidative stress and reducing the dose consumption of erythropoietin.

What is already known about this topic?

It was previously proven that the plasma levels of L-carnitine are reduced in chronic hemodialysis patients, whereas lipid biomarkers of oxidative stress remain high. A few studies have shown that L-carnitine therapy in hemodialysis patients can induce a significant reduction in the level of oxidative stress markers.

What does this study add?

Our findings strongly confirmed that the administration of L-carnitine in ESRD patients undergoing chronic hemodialysis significantly reduced the levels of lipid biomarkers of oxidative stress. Furthermore, L-carnitine therapy significantly reduced the dose consumption of erythropoietin after 5 months without any side effects. In addition, our findings showed a significant inverse correlation between MDA levels and medullary and cortical blood flow, implying that L-carnitine therapy can modulate the adverse effect of MDA-related oxidative stress on renal blood flow, but not significantly.

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Ethics

Ethics Committee Approval: This controlled double-blind randomized clinical trial was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (approval number: IR.AJUMS.REC.1394.79 and IRCT2015112224645N2).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions

Surgical and Medical Practices: S.S., S.S.B.M., H.K., K.H.N., K.A.A., Concept: S.S., S.S.B.M., H.K., K.H.N., K.A.A., Design: S.S., S.S.B.M., H.K., K.H.N., K.A.A., Data Collection or Processing: S.S., S.S.B.M.,

H.K., K.H.N., K.A.A., Analysis or Interpretation: S.S., S.S.B.M., H.K., K.H.N., K.A.A., Literature Search: S.S., S.S.B.M., H.K., K.H.N., K.A.A., Writing: S.S., S.S.B.M., H.K., K.H.N., K.A.A.

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REFERENCES

- Hosseinpanah F, Kasraei F, Nassiri AA, Azizi F. High prevalence of chronic kidney disease in Iran: a large population-based study. *BMC Public Health* 2009; 9: 44.
- Shoji T, Nishizawa Y. Chronic kidney disease as a metabolic syndrome with malnutrition--need for strict control of risk factors. *Intern Med* 2005; 44: 179-87.
- Tsimihodimos V, Dounousi E, Siamopoulos KC. Dyslipidemia in chronic kidney disease: an approach to pathogenesis and treatment. *Am J Nephrol* 2008; 28: 958-73.
- Vaziri ND, Moradi H. Mechanisms of dyslipidemia of chronic renal failure. *Hemodial Int* 2006; 10: 1-7.
- Bellinghieri G, Santoro D, Calvani M, Mallamaci A, Savica V. Carnitine and hemodialysis. *Am J Kidney Dis* 2003; 41(3 Suppl 1): 116-22.
- Arduini A, Bonomini M, Savica V, Amato A, Zammit V. Carnitine in metabolic disease: potential for pharmacological intervention. *Pharmacol Ther* 2008; 120: 149-56.
- Bonomini M, Zammit V, Pusey CD, De Vecchi A, Arduini A. Pharmacological use of L-carnitine in uremic anemia: has its full potential been exploited? *Pharmacol Res* 2011; 63: 157-64.
- Reuter SE, Evans AM. Carnitine and acylcarnitines: pharmacokinetic, pharmacological and clinical aspects. *Clin Pharmacokinet* 2012; 51: 553-72.
- Longo N, Frigeni M, Pasquali M. Carnitine transport and fatty acid oxidation. *Biochim Biophys Acta* 2016; 1863: 2422-35.
- Schreiber B. Levocarnitine and dialysis: A review. *Nutr Clin Pract* 2005; 20: 218-43.
- Safari MR. Free radicals in biological system. Hamadan university of medical sciences publication 2002: 154-170.
- Kim J, Shin W. How to do random allocation (randomization). *Clin Orthop Surg* 2014; 6: 103-9.
- Dujardin M, Luybaert R, Vandenbroucke F, Van der Niepen P, Sourbron S, Verbeelen D, et al. Combined T1-based perfusion MRI and MR angiography in kidney: first experience in normals and pathology. *Eur J Radiol* 2009; 69: 542-9.
- Paul JL, Sall ND, Soni T, Poignet JL, Lindenbaum A, Man NK, et al. Lipid peroxidation abnormalities in hemodialyzed patients. *Nephron* 1993; 64: 106-9.
- Loughrey CM, Young IS, Lightbody JH, McMaster D, McNamee PT, Trimble ER. Oxidative stress in haemodialysis. *QJM* 1994; 87: 679-83.
- Brenner BM, Rector FC. *Brenner and Rector's the Kidney*. 8rd ed. Philadelphia: Saunders Elsevier; 2008. P. 1889-93.
- Bloch AS, Shils ME. Appendices. In: Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ, editors. *Modern Nutrition in Health and Disease*. 10 rd ed. Philadelphia: Lippincott Williams & Wilkins; 2006. p.1896.
- Evans A. Dialysis-related carnitine disorders and levocarnitine pharmacology. *Am J Kidney Dis* 2003; 41(Suppl 4): 13-26.
- Fatouros IG, Douroudos I, Panagoutsos S, Pasadakis P, Nikolaidis MG, Chatzinikolaou A, et al. Effects of L-carnitine on oxidative stress responses in patients with renal disease. *Med Sci Sports Exerc* 2010; 42: 1809-18.
- Safari MR, Isfahani M, Sheikh N. The Study of Hemodialysis Effectiveness on the Change Rate of Lipid Peroxidation and L-Carnitine Level in Hemodialysis Patients. *EJIFCC* 2010; 21: 24-9.
- Emami Naini A, Moradi M, Mortazavi M, Amini Harandi A, Hadizadeh M, Shirani F, et al. Effects of Oral L-Carnitine Supplementation on Lipid Profile, Anemia, and Quality of Life in Chronic Renal Disease Patients under Hemodialysis: A Randomized, Double-Blinded, Placebo-Controlled Trial. *J Nutr Metab* 2012; 2012: 510483.
- Kudoh Y, Aoyama S, Torii T, Chen Q, Nagahara D, Sakata H, et al. Hemodynamic stabilizing effects of L-carnitine in chronic hemodialysis patients. *Cardiorenal Med* 2013; 3: 200-7.