Can L-Carnitine Supplementation Improve Cardiopulmonary Function? A Randomized Controlled Clinical Trial in Hemodialysis Patients

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Original Paper

Introduction. L-Carnitine is a cardioprotective agent which balances metabolism by promoting mitochondrial β -oxidation and facilitating transportation of long chain fatty acids into the mitochondrial matrix. It has been shown that L-Carnitine level in plasma and tissue is lower in hemodialysis patients and they may lose the benefits of this substance. The aim of this trial was to evaluate the effects of L-Carnitine supplementation on cardiorespiratory Function in hemodialysis patients through ergospirometry.

Methods. The current study was conducted on 46 chronic hemodialysis patients. The patients were divided into two groups. In both groups ergospirometry parameters (VE Max, VO2-Max and VCO2 Max, AT, VE/VCO2 Slope) were recorded for a 3-month period of time. During this period, one group received L-Carnitine at doses of 2 g/d orally and the other group received only placebo. After three months, all of the mentioned parameters reevaluated and statistical analysis was done.

Results. Only CRP value was different between two group and in placebo group increased significantly after 3 months ($P < .05$). No significant difference was detected in Cardio-respiratory factors. In terms of ergospirometry, PET-CO2 was the only parameter which was significantly increased in the treatment group but decreased in placebo group ($P < .05$).

Conclusion. Significant differences between our groups showed that L-Carnitine could help hemodialysis patients with cardiopulmonary problems to suffer lower rate of inflammation and poor life quality as shown at least in comparison of the two factors including CRP and PETCO2 at rest.

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INTRODUCTION

L-Carnitine (3-hydroxy-4-N-trimethylbutyric acid) is an important agent in membrane transportation of acyl- CoA compounds. As it acts mainly through intramitochondrial transportation of long-chain fatty acids; it seems to be essential for mitochondrial ß-oxidation of the named compounds.[1] It is worth pointing out that fatty acids are key constructive sources for muscles like myocardial muscle and lack of serum carnitine level may lead to muscular weakness and consequent cardiomyopathy, heart failure, and other serious complications[2] in this matter. L-Carnitine as acylcarnitine form play also a key role in eliminating of some toxic metabolites which are finally excreted in urine.[3] Studies have figured

out that patients who are on hemodialysis have a decreased serum and tissue carnitine concentration due to its diminished synthesis by kidney in addition to excessive loss across the dialysis membrane through hemodialysis.[4] The ratio of free carnitine and acylcarnitine usually falls in these patients due to compromised acylcarnitine elimination to consequently worsening detoxification of acids.[5] L-Carnitine supplementation has recently been shown to improve hemoglobin and hematocrit levels among end stage renal disease patients and could lessen their need to erythropoietin.[6,7] Additionally, physical performance and the morphology of the type I and IIa fibers of the skeletal muscles have been found to be improved in the patients who took named supplements.[8] Other studies also reported the beneficial effects of L-Carnitine supplementation on cholesterol and triglyceride levels.[9] To our knowledge, the effects of L-Carnitine on Cardiopulmonary function have not been evaluated by ergospirometry so far. cardiopulmonary exercise test (CPET) can successfully predict the situation of cardiac and pulmonary function as well as other metabolic and general condition using some parameters like SpO2, VO2/kg, VE/VCO2, AT, end-tidal PCO2 (PET-CO2), etc. The aim of this randomized placebo clinical trial was to evaluate the effects of L-Carnitine supplementation on cardiopulmonary function in hemodialysis patients through ergospirometry. In addition, we planned to evaluate the effects of L-Carnitine supplementation on some of inflammatory markers.

MATERIALS AND METHODS

Study Design

This randomized clinical trial was conducted in Masih Daneshvari hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. This study was done between January 2017 and January 2018.

Inclusion and Exclusion Criteria

Based on the effect size of previous studies by consideration $\alpha = 0.05$ and $\beta = 0.2$, the sample size of this study was estimated as 50 patients and totally 60 patients included in the study. The inclusion criteria of this study were as follows: patients who were on hemodialysis for at least three previous months and who had no history of cardio-pulmonary diseases or any disability condition were included and patients who were not able to do their routine physical activities, patients with unstable clinical conditions, those with hemoglobin level lower than 9 mg/L and peripheral oxygen saturation lower than 70% were excluded.

Allocation and Randomization

The patients who meet the inclusion criteria were allocated into two equal groups based on the simple randomization through using computer-generated random digit numbers.

Protocol of Intervention

The patients who were in treatment group received 1000 mg of oral L-Carnitine twice daily for three months. L-Carnitine tablets were manufactured in Iran by "Karen" ® company. The patients who were in placebo group, received a placebo tablet same as treatment group. The placebo was similar to the L-Carnitine tablet in point of shape, smell and color. All the participants in both groups received 6000 IU/week erythropoietin as routine treatment for anemia.

Cardiopulmonary Exercise Test (CPET)

CPET was done on the day of hemodialysis immediately before doing it. The test was done considering RAMP protocol through incremental exercise test to symptom-limited maximum with starting load suitable for individual condition rising gradually to achieve respiratory exchange ratio (RER) of at least 1.15. All the participants were physically examined by single pulmonologist before placing on the cycle. Twelve-lead electrocardiography monitored the ischemic events or any arrhythmia in cardiovascular tract. Meanwhile, SPO2 was monitored to warn any respiratory problem. The participants were advised to continue the test until exhaustion to get the best results. They also were advised to finish the test if they suffered from ischemia-related chest pain, lightheadedness, dizziness, faint, systolic blood pressure fall > 20 mmHg, muscle pain, and any other condition needing to urgent critical intervention.

Outcome Measure

The demographic characteristics of the patients were gathered through medical history and an

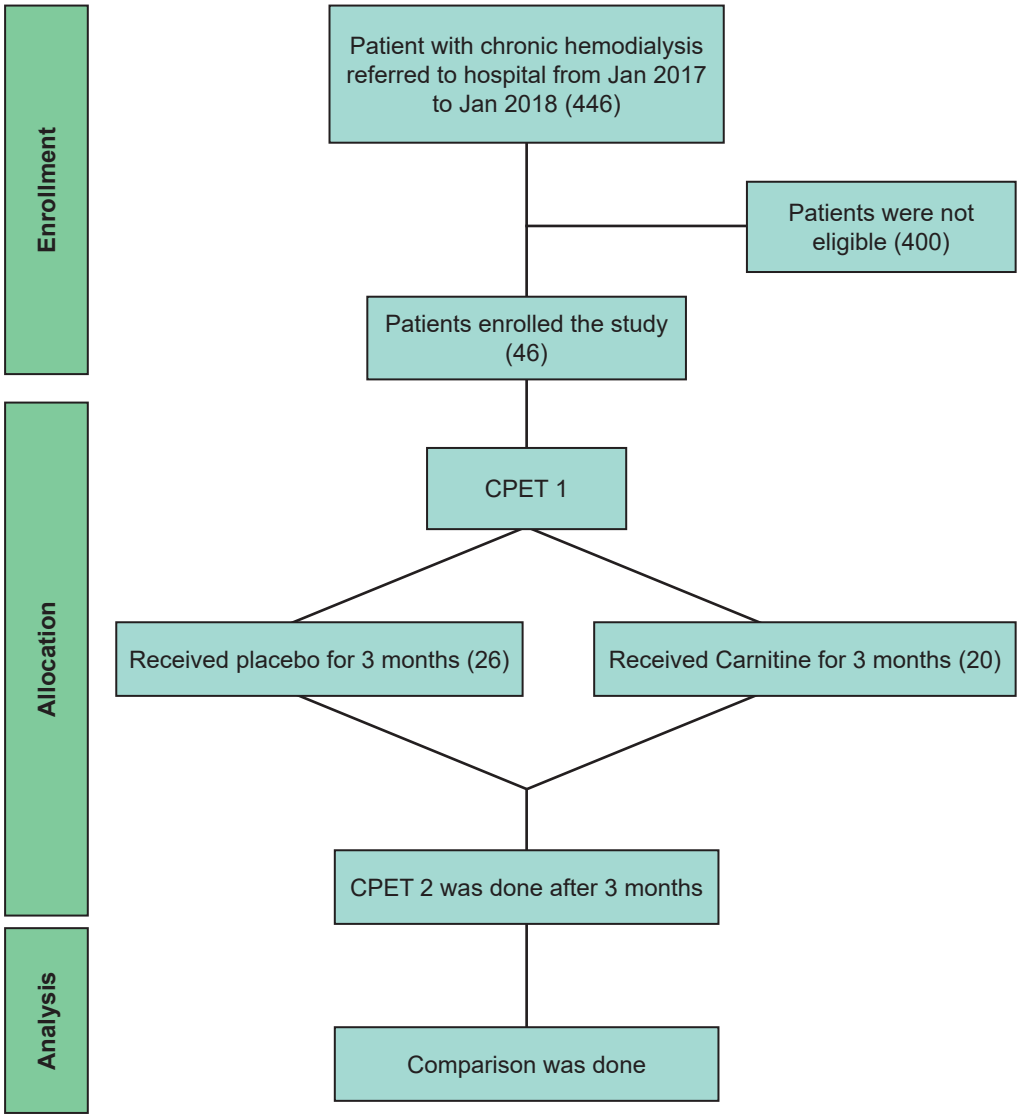
exact medical examination. At baseline and at the end of the study, cardiopulmonary function was assessed through ergospirometry as the primary outcome. The participants were visited by single nephrologist three times a week on their day of hemodialysis throughout the study for blood pressure and general condition. In addition, some markers such as serum parathormone (PTH), arterial O2 saturation (SpO2), serum albumin, ESR, CRP, hemoglobin (Hb), and ferritin were measured as secondary outcomes.

Statistical Analysis

The gathered data were imported into SPSS software version 23 (IBM, USA). Variables were presented as proportion and continuous variables as mean ± SD as well as other central indices. Kolmogorov-Smirnov test was used to determine if the data follows normal distribution. To compare quantitative data before and after intervention, either paired t-test (for parametric variables) or Wilcoxon (for non-parametric variables) was utilized. The significant level was considered equal or lower than .05 and results reported as mean ± standard division (SD). This study used 95% confidence interval and $\alpha = 0.05$ as type one error to achieve 0.8 power.

Ethical Considerations

The ethical committee of Shahid Beheshti



The CONSORT (Consolidated Standards of Reporting Trials) Diagram of the Current Study

University of Medical Sciences approved the design of this study in point of ethical aspects under the code: "Ir.sbmu.nritld.rec.1394.590". In addition, the settings of this current trial registered in Iranian clinical Trial Registry (IRCT20161219031464N3). All the participants were explained about the aim and the process of the study before giving their written consents. There was no extra charge for the tests and medications which the study needs to use and all the individual information are kept safely by the principal investigators.

RESULTS

Totally 46 patients enrolled this study (20 patients in treatment group and 26 patients in control group) and completed it. The CONSORT diagram of the current study is shown in Figure. The demographic data are summarized in Table 1. Based on the results there were no significant statistical differences between the two groups in terms of demographic variables. For cardiopulmonary function assessed by ergospirometry, the results did not show any significant differences before and after supplementation, except for PETCO2-rest ($P < .05$) which increased up to 1.2 after using L-Carnitine whilst a 1.6 reduced value in the control group. The ergospirometry results can be seen in Table 2.

In respect of secondary outcomes which aimed to assess some markers such as CRP, albumin, PTH, and ferritin; these results showed that CRP increased significantly in placebo group after L-Carnitine supplementation which was not seen in the treatment group. Results could be found in Table 3.

Table 1. The Comparison of Demographic, Clinical, and Para Clinical Characteristics Among Intervention and Placebo Groups

Variable	Intervention	Placebo	*P*
Age	48.65 ± 13.91	45.30 ± 14.33	> .05
Sex			
Female	5 (25)	11 (42.3)	> .05
Male	15 (75)	15 (57.7)	
BMI, kg/m^2	38.8 ± 14.1	34.8 ± 12.6	> .05
Erythropoietin, UI*			
No Use	3 (15)	2 (7.7)	> .05
2000	11 (55)	13 (50)	
4000	6 (30)	11 (42.3)	
CKD Causes			
Diabetes	4 (20)	6 (23.1)	> .05
Kidney Stone	-	5 (19.2)	
Hypertension	6 (30)	7 (26.9)	
Glomerulonephritis	1 (5)	1 (3.8)	
Others	9 (45)	7 (26.9)	
Dialysis Vintage			
3 to 12 months	2 (10)	2 (7.7)	> .05
1 to 5 years	11 (55)	15 (57.7)	
> 5 years	7 (35)	9 (34.6)	
Access Type			
Temporary	-	1 (3.8)	> .05
Permanent	2 (10)	2 (7.7)	
Arteriovenous Fistula	17 (85)	23 (88.5)	
Arteriovenous Graft	1 (5)	-	
Underlying Diseases			
Diabetes	2 (10)	3 (11.5)	> .05
Hypertension	12 (60)	12 (46.2)	
Heart Failure	1 (5)	9 (34.6)	
Others	5 (25)	2 (7.7)	
Smoking			
Yes	16 (80)	23 (88.5)	> .05
No	4 (20)	3 (11.5)	

*Unit International
BMI, body mass index; CKD, chronic kidney diseases

DISCUSSION

This randomized placebo clinical trial was designed to investigate the effects of L-Carnitine supplementation on cardiorespiratory function in hemodialysis patients. The variables of this study were assessed by ergospirometry and some inflammatory markers. Ergospirometry is a diagnostic procedure which continuously measures respiration and gas metabolism during cardiopulmonary exercise. It simply assesses the function and performance capacity of the cardiopulmonary system as well as body metabolism. Ergospirometry uses some parameters to reveal cardiopulmonary function among patients with relevant medical conditions among which PETCO2 needs to be more explained because it was significantly differ comparing before and after L-Carnitine supplement prescription for the interventional group through the current study. PETCO2 is a predicting factor for ventilation-perfusion in lungs which could indirectly reflect person's cardiac function. It ranges usually 36 to 42 mmHg although this range may be flexible. However, its abnormal values show disease severity in heart failure, cardiomyopathy, pulmonary hypertension, COPD, and restrictive pulmonary diseases.[10] In the current study, PETCO2-rest not only increased in L-Carnitine group, but also decreased in the other group used placebo. Decreased PETCO2-rest may show the severity

Table 2. The Results of Cardiopulmonary Test Through Ergospirometry Test

Variable	Treatment		Placebo		*P*
	Before	After	Before	After	
SPO2	93.2 ± 4.3	95.7 ± 2.3	90.2 ± 5.7	93.5 ± 4.18	> .05
SPO2-rest	94.6 ± 2.01	94.6 ± 2.43	93.3 ± 3.7	92.2 ± 4.7	> .05
SBP	203.7 ± 32.7	212.05 ± 31.2	206.7 ± 29.7	207.04 ± 32.4	> .05
SBP-rest	134.1 ± 24.5	139.8 ± 24.8	138.1 ± 22.7	140.3 ± 19.7	> .05
HRR	45.5 ± 25.02	45.3 ± 21.9	45.2 ± 19.8	41.04 ± 20.8	> .05
VE/VCO2	33.5 ± 3.7	32.3 ± 2.9	30.6 ± 4.4	31.9 ± 7.5	> .05
VE/VCO2 Slope	33.04 ± 4.9	31.4 ± 3.2	32.8 ± 5.8	31.1 ± 5.4	> .05
PETCO2-rest	29.4 ± 3.1	30.6 ± 2.11	29.8 ± 4.1	28.2 ± 4.01	< .05
PETO2-rest	88.5 ± 4.1	85.1 ± 5.6	88.2 ± 4.5	83.6 ± 4.3	> .05
VO2	48.7 ± 12.7	40.7 ± 5.5	51.2 ± 13.7	40.4 ± 7.6	> .05
VO2/Ref	34.6 ± 8.2	27.9 ± 9.3	34.7 ± 13.8	26.04 ± 6.2	> .05
VO2/kg	16.2 ± 5.1	16.4 ± 5.2	17.3 ± 7.9	15.2 ± 3.5	> .05
VO2/wr	11.7 ± 3.3	11.9 ± 2.5	11.6 ± 2.7	13.3 ± 4.01	> .05
O2 Pulse	8.9 ± 2.4	8.4 ± 1.9	9.3 ± 2.3	8.2 ± 1.7	> .05
VCO2	78.4 ± 14	76.3 ± 6.6	72.3 ± 12.4	72.7 ± 8.7	> .05

SpO2, blood oxygen saturation; SBP, systolic blood pressure; HRR, heart rate recovery; VE/VCO2, the minute ventilation/carbon dioxide production; PETCo2-rest, the resting partial pressure of end-tidal carbon dioxide; PETCo2-rest, the resting partial pressure of end-tidal oxygen; VO2, maximum rate of oxygen consumption; VO2/wr, VO2 per work rate; VCO2, carbon dioxide output

Table 3. Comparison of Some Serum Markers Between the Groups of Control and Intervention

Variable	Placebo		Treatment		*P*
	Before	After	Before	After	
CRP	11.1 ± 8.4	15.7 ± 15.4	18.07 ± 12.19	18.1 ± 12.1	< .05
ALB	4.17 ± 0.61	4.18 ± 0.55	3.8 ± 0.46	3.7 ± 0.42	> .05
PTH*	109.5 ± 102.6	133.8 ± 113.7	411.4 ± 307.3	369.3 ± 232.9	> .05
Ferritin	485.3 ± 295.5	430.2 ± 282.5	375.4 ± 258.7	309.3 ± 209.3	> .05

CRP, C reactive protein; ALB, albumin; PTH, parathyroid hormone
*Normal range of PTH is considered usually 150 to 300.

of cardiopulmonary problems and our finding supports the beneficial effect of L-Carnitine in terms of cardiopulmonary function as expected by the investigators. The results of ergospirometry showed that most of the other measured parameters in the treatment group improved but unlike PETCO2-rest, this improvement was not statistically significant. Despite no or rare researches on PETCO2 and CRP changes resulted by L-Carnitine, Kaneko *et al.* reported in 2018 that intravenous L-Carnitine administration can dramatically improve cardiac dysfunction through studying myocardial fatty acid metabolism through[1,2,3] I-labeled β-methyl-p-iodophenyl-pentadecanoic acid and single-photon emission computed tomography.[11] Likely, Sgambat *et al.* studied the effects of intravenous L-Carnitine supplementation on cardiac strain rate in 2012 among chronic hemodialysis children. They concluded that L-Carnitine supplementation could improve carnitine levels, the acylcreatinine/free creatinine ratio, and longitudinal strain rate in children who were on hemodialysis.[12] Matsumoto *et al.* were another research team in 2000 to assess the effects of low dose L-Carnitine supplementation (500 mg/d) on chest symptoms and left ventricular (LV) mass in hemodialysis patients to figure out that low-dose L-Carnitine could improve the cardiac morbidity by restoring decreased tissue carnitine levels and impaired oxidation of free fatty acids.[13] Another finding of the current study was the beneficial effects of oral L-Carnitine supplement on inflammatory markers. The inflammatory markers were controlled from rising in the treatment group. Among inflammatory markers, CRP increased significantly in the placebo group while having no obvious change in the treatment group. The results demonstrated that CRP was brightly controlled significantly in patients who received L-Carnitine. Increased circulating levels of CRP, as an inflammatory factor, have been proposed to act as an independent predictor of cardiovascular diseases and atherothrombotic events. Accordingly,

CRP can be considered as one of the best known markers of systemic inflammation. Through a meta-analysis in 2015 regarding the effects of L-Carnitine supplementation on circulating CRP levels, Sahebkar revealed that L-Carnitine could lessen the levels of CRP to be clinically helpful in cardiovascular conditions.[14] To the best of our knowledge, the current study is the first one in which the effects of L-Carnitine on cardiorespiratory function was evaluated through ergospirometry among hemodialysis patients. The results of the current study suggest that L-Carnitine supplementation can improve PET-CO2-rest and serum CRP levels as cardiopulmonary parameter and inflammatory factor, respectively; in hemodialysis patients at least in CPET. If L-Carnitine is able to block CRP induction in the body, it would be an amazing way to control inflammation in human disregarding the causes. Unfortunately, other inflammation predictors were not controlled by the supplement and the majority of them were not measured through the current study to achieve the optimum conclusion in this regard. So, it would be worth working on the matter by the future studies.

CONCLUSION

To sum up, significant differences between our groups showed that L-Carnitine could help hemodialysis patients with cardiopulmonary problems to suffer lower rate of inflammation and poor life quality as shown at least in comparison of the two factors including CRP and PETCO2 at rest.

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