

Associations of oral L-carnitine with hemoglobin, lipid profile, and albumin in hemodialysis patients

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BACKGROUND: Previous reports have suggested acute phase proteins, such as albumin, to alter in hemodialysis (HD) patients. Intravenous L-carnitine supplementation is expected to improve the level of plasma albumin in HD patients. This study was performed to evaluate the effects of oral L-carnitine supplementation on hemoglobin, lipid profile, and albumin in HD patients. **METHODS:** In a double-blind, placebo-controlled study during October 2008 to April 2010, 54 HD patients were randomly assigned into 3 groups to receive 750 mg/day oral L-carnitine (17 patients), placebo (19 patients), or nothing (control group, 18 patients) for 6 months. Eligible patients for the study were above 21 years old, had no carnitine during the previous month, and had signed the informed consent to enter the study. The primary outcome was plasma albumin level. The secondary outcomes were hemoglobin level, erythropoietin (EPO) doses, lipid profile [high-density lipoprotein (HDL), low-density lipoprotein (LDL), cholesterol, and triglyceride], and side effects of L-carnitine. Patients were followed for side effects. **RESULTS:** Before administration of L-carnitine, the mean levels of hemoglobin were 10.81 ± 1.20 mg/dl in the L-carnitine group, and 9.85 ± 1.13 mg/dl in the placebo group. At the end of the study, hemoglobin level was 11.6 ± 1.05 mg/dl in the L-carnitine group and 10.33 ± 1.08 mg/dl in the placebo group. Therefore, hemoglobin levels rose significantly in the L-carnitine group ($p = 0.04$) but not in the placebo group ($p > 0.05$). HDL decreased in the placebo group but had no changes in the L-carnitine group. Cholesterol, triglyceride, and LDL did not change during 6 months ($p > 0.05$). Side effects did not increase in the L-carnitine group. **CONCLUSIONS:** Administration of 750 mg/day oral L-carnitine for 6 months had beneficial effects on hemoglobin and HDL, but not on albumin and the required EPO. Studies with higher doses of oral L-carnitine or in peritoneal dialysis patients are suggested.

KEYWORDS: L-Carnitine, Kidney Failure, Chronic, Acute-Phase Proteins

BACKGROUND

Cardiovascular diseases are the most common cause of mortality in chronic renal failure.^[1] Recent studies have shown chronic inflammation as the main cause of malnutrition, cardiovascular diseases, and atherosclerosis in end-stage renal disease (ESRD) patients.^[2,3] C-reactive protein (CRP), interleukin 6 (IL-6) and albumin plasma levels are known to be predictors of malnutrition, cardiovascular diseases, and mortality in these patients.^[4] Previous reports have suggested alterations of acute phase proteins such as albumin in hemodialysis (HD) patients.^[5]

There is a reverse correlation between albumin and CRP levels. Low albumin is associated with malnutrition. Albumin is also influenced by inflammation and infection.^[6]

Carnitine contains 2 amino acids (methionine and lysine) and helps long chain fatty acids to transfer into mitochondria. Moreover, carnitine is

essential in the metabolism of fatty acids, especially in cardiac and skeletal fibers.^[7,8]

Carnitine passes from dialysis membrane more than normal renal clearance.^[9] Patients who undergo HD for long time seem to have carnitine deficiency.^[10]

Previous studies have reported the benefits of intravenous carnitine on albumin, CRP,^[11] transferrin, hemoglobin, body mass index (BMI),^[12] triglyceride,^[13] illness, exercise tolerance,^[14] quality of life,^[15] ventricular hypertrophy,^[16] and length of hospital stay.^[17]

Intravenous L-carnitine supplementation is expected to suppress inflammation and improve the level of plasma albumin in HD patients.^[18] The aim of this study was to understand the effects of oral L-carnitine supplementation on plasma albumin in HD patients.

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METHODS

This was a placebo-controlled, double-blind, randomized clinical trial. The study population included all HD patients in Alzahra, Shariati, and Saidi HD centers (Isfahan, Iran). A sample group of 54 patients was selected by simple non-random sampling. The patients and laboratory staff were blinded to randomization. The participants were divided into 3 groups of carnitine (n = 17), placebo (n = 19), and control (n = 18) using statistical randomization methods. While the first and second groups received oral L-carnitine and placebo tablets, respectively, the control group did not receive any intervention.

All participants signed informed consents. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences (Isfahan, Iran) and registered in the Iranian Registry of Clinical trials (IRCT ID: IRCT138804092106N1). Patients who entered the study were followed from October 2008 to April 2010.

Inclusion criteria were being older than 21 years of age, having history of HD at least for one month, providing an informed consent, no history of carnitine use in the previous 8 weeks, and no history of infectious diseases or fever in the previous month.

Exclusion criteria were experiencing side effects (hypertension, dizziness, blurred vision, decreased mini-mental state score, and diarrhea) after taking tablets, not willing to cooperate, having an infectious problem or antibiotic usage, changed dialysis method, continuing treatment in another center, or having renal transplantation. The latest available data from the excluded patients was registered and analyzed.

Demographic variables, history of cardiovascular problems, diabetes mellitus, malignancy, and liver disease, and length of dialysis were recorded in a form by trained staff.

L-carnitine and placebo tablets were provided by Pars Mino company (Tehran, Iran) and were the same in size, color, weight (250 mg), and box. Drug or placebo was administered to patients as 3 oral tablets per day, in divided doses, for 6 months. The control group received no L-carnitine or placebo. If the patients had vomiting 30 minutes after taking a tablet, it was administered again.

The primary outcome was plasma albumin level. The secondary outcomes were hemoglobin level, eryt-

thropoietin (EPO) doses, lipid profile including high density lipoprotein (HDL), low density lipoprotein (LDL), cholesterol, and triglyceride, and side effects of L-carnitine. Plasma albumin level (detected by bromocresol green method) was checked at the beginning of the study and every month before dialysis sessions. All patients paid monthly visits to the nephrology clinics for the side effects to be checked and the laboratory data to be evaluated.

At the end of the study, all collected data was analyzed by SPSS¹⁷ (SPSS Inc., Chicago, IL) using analysis of variance (ANOVA), paired t-test, chi-square test, and repeated measures general linear model (GLM). P-values less than 0.05 were considered to be significant.

RESULTS

A total number of 54 patients, including 26 women (48.1%) and 28 men (51.9%), participated in this study. The mean age of patients was 54 ± 17 years. The mean length of dialysis was 36 ± 33 months.

History of cardiovascular diseases, diabetes mellitus, and other diseases (such as glomerulonephritis, polycystic kidney disease, and urologic problems) was observed in 20 (37%), 14 (25%), and 7 patients (13.7%), respectively. Age, sex, and length of dialysis were not significantly different between the 3 groups ($p > 0.05$).

In total, 15 patients were excluded from the study due to renal transplant (3 in the first month and 1 in the 5th month), changed dialysis center after the first month (1 patient), infection and antibiotic administration at the 3rd month (1 patient), gastrointestinal side effects such as vomiting or diarrhea (5 patients), decreased mini-mental state score (1 patient), and death (3 patients).

The mean follow-up duration was 3.7 ± 2.2 months. The 3 groups were not different in the length of follow-up period ($p > 0.05$).

Before administration of L-carnitine, the mean albumin level was 4.14 ± 0.42 mg/dl in the carnitine group, 4.21 ± 0.41 mg/dl in the placebo group, and 3.96 ± 0.45 mg/dl in the control group. There was no significant difference between the 3 groups in terms of baseline albumin level ($p > 0.05$). The corresponding values at the end of the study were 4.36 ± 0.53 , 4.41 ± 0.72 , and 3.84 ± 0.45 mg/dl. Changes of albumin levels from the beginning to the end of the study were

0.27 ± 0.60 mg/dl in the carnitine, 0.13 ± 0.65 mg/dl in the placebo, and -0.06 ± 0.68 mg/dl in the control group (Figure 1).

Repeated measures GLM showed no significant difference in albumin changes between the 3 groups, before and after the study ($p > 0.05$).

In the carnitine group, 1 patient had diarrhea (5.9%) and 2 had vomiting (11.8%). In the placebo group, 2 patients had diarrhea (11.8%) and 1 patient had decreased mini-mental state score. One patient in the carnitine group and 2 patients in the placebo group died. Fisher's exact test showed no significant difference in side effects and mortality between the 2 groups ($p > 0.05$).

Baseline hemoglobin level was 10.81 ± 1.20 mg/dl in the carnitine group and 9.85 ± 1.13 mg/dl in the placebo group. There was no significant difference in baseline hemoglobin levels between the two groups ($p > 0.05$).

We also evaluated the lipid profile in the carnitine and placebo groups. Hemoglobin, EPO, and lipid profile values are summarized in table 1.

DISCUSSION

In this study, we found no increase in plasma albumin concentration after administration of oral L-carnitine. Duranay et al. could find significant increase of plasma albumin level by administration of 20 mg/kg intravenous carnitine. They had 21 patients in the experiment group and 21 in the control group (but no placebo group).^[18] Argani et al. administered 500 mg oral carnitine to 40 patients for 2 months. They reported significant increase in plasma albumin levels as a result of carnitine intake.^[19] In another study, intravenous carnitine was administered to 48 patients (20 mg/kg, 3 times per week for 6 months). On the other hand, a group of 65 patients received placebo. The carnitine group had significant increases in albumin, transferrin, and CRP. Another study on 28 HD survivors used 15 mg/kg L-carnitine after every HD session for 6 months. They were compared with 25 non-treated patients. No changes in plasma albumin, anthropometric scales, after-dialysis weight, food consumption, and creatinine were seen.^[20] Trovato et al. compared 25 treated patients (by 1g L-carnitine) with 35 non-treated patients. They suggested higher levels of plasma albumin and

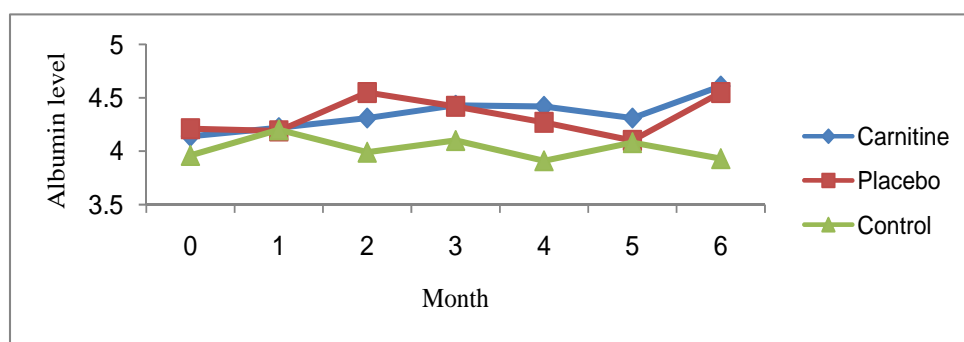


Figure 1. The mean of plasma albumin concentrations (mg/dl) in the carnitine, placebo, and control groups during 6 months ($p > 0.05$)

Table 1. Hemoglobin, erythropoietin (EPO), cholesterol, triglyceride, high density lipoprotein (HDL), and low density lipoprotein (LDL) before and after administration of L-carnitine (Data is reported as mean ± SD.)

	Baseline	3 rd month	6 th month	P-value
Hemoglobin (Carnitine group)	10.81 ± 1.20	11.07 ± 1.05	11.60 ± 1.05	0.04
Hemoglobin (Placebo group)	9.85 ± 1.13	10.42 ± 1.35	10.33 ± 1.08	> 0.05
EPO dose (Carnitine group)	7400 ± 5168	5777 ± 4521	6666 ± 4618	> 0.05
EPO dose (Placebo group)	6018 ± 4874	4800 ± 4638	6125 ± 4421	> 0.05
Cholesterol (mg/dl) (Carnitine group)	133.72 ± 44.51	127.30 ± 40.12	135.00 ± 43.47	> 0.05
Cholesterol (mg/dl) (Placebo group)	154.72 ± 47.52	178.81 ± 74.61	153.45 ± 39.68	> 0.05
Triglyceride (mg/dl) (Carnitine group)	157.36 ± 67.97	149.40 ± 42.18	139.00 ± 53.08	> 0.05
Triglyceride (mg/dl) (Placebo group)	146.18 ± 57.77	162.90 ± 96.01	137.00 ± 64.51	> 0.05
LDL (mg/dl) (Carnitine group)	81.18 ± 33.68	82.80 ± 34.39	78.27 ± 33.85	> 0.05
LDL (mg/dl) (Placebo group)	98.38 ± 31.45	102.43 ± 31.42	88.85 ± 32.16	> 0.05
HDL(mg/dl) (Carnitine group)	33.54 ± 5.78	32.10 ± 8.00	29.77 ± 4.65	> 0.05
HDL (mg/dl) (Placebo group)	42.90 ± 9.52	36.27 ± 8.94	37.09 ± 9.89	0.04

EPO: Erythropoietin; HDL: High density lipoprotein; LDL: Low density lipoprotein

plasma protein in the L-carnitine group.^[21]

This study revealed that administration of 750 mg/day oral L-carnitine increased hemoglobin level during 6 months, but had no beneficial effects on EPO treatment. Sabry failed to establish any changes in hemoglobin levels or EPO need after administration of 1500 mg/day oral L-carnitine during 6 months.^[22] However, the benefits of intravenous administration on hemoglobin and EPO have been previously demonstrated in children^[23] and adults.^[24,25] Wanic-Kossowska et al. recommended the combination therapy of L-carnitine and EPO in chronic renal failure patients.^[26]

Similar to previous studies,^[27] our results confirmed the benefits of oral L-carnitine on lipid profile. Carnitine inhibited HDL reductions even in the first evaluation of HDL in the 3rd month and by lower administered doses.

Despite having proper quality between recent similar studies, this placebo-controlled, double-blind randomized research could not show any increases in albumin levels after oral administration of L-carnitine. In addition, it could not attribute any side effects to L-carnitine administration.

Bioavailability of oral L-carnitine has been estimated as about 14-18%.^[28] Since L-carnitine can pass thorough dialysis membrane,^[29] we assume that the oral dose is not enough to have an ideal effect. However, we administered 250 mg oral tablets 3 times per day. We therefore suggest higher doses with at least 1-gram tablets per day for HD survivors. Administration of L-carnitine in peritoneal dialysis survivors is also recommended for further studies.

Some patients claimed increased appetite. This was not the aim of this study, but can be reviewed over similar studies.

We lost many cases during the study due to the long period of the study. Because the half life of albumin is approximately 20 days,^[30] shorter studies with larger sample size would reveal further details.

CONCLUSION

Administration of 750 mg oral L-carnitine per day could not improve plasma albumin concentration and doses of EPO. However, hemoglobin and HDL levels were improved. No side effects could be attributed to oral L-carnitine administration.

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