Saudi J Kidney Dis Transpl 2012;23(3):484-498


**Saudi Journal of Kidney Diseases and Transplantation**

***Original Article***

# Oral Carnitine Supplementation for Dyslipidemia in Chronic Hemodialysis Patients

Afsoon Emami Naini[1], Masoumeh Sadeghi[2], Mojgan Mortazavi[1], Mojdeh Moghadasi[1], Asghar Amini Harandi[3]

[1]Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, and [2]Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan; [3]Jahrom University of Medical Sciences, Jahrom, Iran

**ABSTRACT.** Carnitine deficiency is a commonly observed problem in maintenance hemodialysis (MHD) patients, which results in altered metabolism of fatty acids and subsequently development of dyslipidemia. To evaluate the effect of oral L-carnitine (LC) supplementation on lipid profile of adult MHD patients, we studied 30 of them (19 males, 11 females) who received LC supplementation of 250 mg tablets three times a day for eight weeks. They were compared with 30 matched patients as a control group. Serum lipid profiles were compared before and after the intervention between the two groups. There was a significant decrease of the values of the lipid profile in the intervention group before and after carnitine supplementation including the mean values of total cholesterol (190 ± 36.8 vs. 177 ± 31.2 mg/dL), triglyceride (210 ± 64.7 vs. 190 ± 54.1 mg/dL) and LDL-cholesterol (117 ± 30.1 vs. 106 ± 26.3 mg/dL), while the values did not change siginificantly from base line in the control group. However, the difference for HDL-cholesterol in intervention group was not statistically significant. None of the patients dropped out of the study due to drug side effects. Oral LC supplementation (750 mg/day) is able to improve lipid profile in patients on MHD. Further long-term studies with adequate sample size are needed to define the population of patients who would benefit more from carnitine therapy and the optimal dose and the most efficient route for administration of the drug.

## Introduction

Dyslipidemia is found in approximately 45 to 50 percent of maintenance hemodialysis patients (MHD),[1] and has been proposed as a major cardiovascular risk factor in these patients.[2] Carnitine is an important element in the beta-oxidation of fatty acids and reduces free fatty acid availability for triglyceride synthesis.[3,4] Therefore, its deficiency in MHD patients may worsen the dyslipidemia. Moreover, in end-stage renal disease (ESRD) there is an increased demand for free carnitine in response to hypoxemia or acidosis.[5]

Carnitine deficiency is commonly seen in MHD patients.[5] Carnitine depletion may result from increased clearance during hemodialysis,

Correspondence to:

Dr. Afsoon Emami Naini,
Isfahan Kidney Diseases Research Center,
Isfahan University of Medical Sciences,
Isfahan, Iran
E-mail: af_emami@med.mui.ac.ir

Table 1. Lipid profile before and after carnitine supplementation.

| Total (n = 30 in each group) | | | | Intervention group | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Men (n = 19) | | | Women (n = 11) | | |
| **Data** | **Before** | **After** | ***P*** | **Before** | **After** | ***P*** | **Before** | **After** | ***P*** |
| TC (mg/dL) | | | | | | | | | |
| Intervention group | 189.8 ± 36.8 | 176.6 ± 31.2 | <0.01 | 187.7 ± 38.1 | 171.2 ± 33.1 | <0.01 | 193.4 ± 36.1 | 185.9 ± 26.4 | 0.32 |
| Control group | 195.4 ± 33.2 | 193.2 ± 35.5 | | | | | | | |
| TG (mg/dL) | | | | | | | | | |
| Intervention group | 209.5 ± 64.7 | 186.8 ± 54.1 | <0.001 | 208.6 ± 65.9 | 178.7 ± 50.5 | <0.01 | 211.2 ± 65.6 | 200.7 ± 59.6 | 0.16 |
| Control group | 189.4 ± 40.0 | 193.5 ± 44.9 | | | | | | | |
| HDL-c (mg/dL) | | | | | | | | | |
| Intervention group | 33.4 ± 9.9 | 34.3 ± 7.6 | 0.26 | 34.4 ± 10.9 | 35.1 ± 8.6 | 0.50 | 31.8 ± 7.9 | 32.9 ± 5.7 | 0.30 |
| Control group | 32.5 ± 8.1 | 33.0 ± 7.8 | | | | | | | |
| LDL-c (mg/dL) | | | | | | | | | |
| Intervention group | 116.7 ± 30.1 | 106.0 ± 26.3 | <0.01 | 112.3 ± 30.1 | 99.8 ± 27.6 | <0.01 | 124.2 ± 29.9 | 116.8 ± 20.6 | 0.20 |
| Control group | 113.7 ± 22.3 | 115.7 ± 24.9 | | | | | | | |
| TC >200 mg/dL (%) | 11 (36.7) | 6 (20.0) | | 8 (42.1) | 3 (15.6) | | 3 (27.3) | 3 (27.3) | |
| TG >150 mg/dL (%) | 27 (90.0) | 21 (70.0) | | 17 (89.5) | 13 (68.4) | | 10 (90.9) | 8 (72.7) | |
| HDL-c >35 mg/dL (%) | 22 (72.7) | 16 (53.3) | | 14 (73.7) | 10 (52.6) | | 8 (72.7) | 6 (54.5) | |
| LDL-c >100mg (%) | 19 (63.3) | 21 (70.0) | | 12 (63.2) | 12 (63.2) | | 7 (63.6) | 9 (81.8) | |

TC: Total cholesterol, TG: Triglyceride, LDL-c: Low Density Lipoprotein-cholesterol, HDL-c: High Density Lipoprotein-cholesterol

intestinal malabsorption, increased carnitine requirements, or reduced renal synthesis.[3,6] However, it has been demonstrated that carnitine deficiency will progress in MHD patients over time.[7,8] The results of previous studies testing the effects of carnitine supplementation on lipid profile are conflicting.[6,9-12] Furthermore, data on the efficacy of oral L-carnitine (LC) are limited. This study was conducted to evaluate the effect of oral LC supplementation on lipid profile of adult MHD patients.

## Materials and Methods

In a controlled clinical trial, a total of 30 patients (19 males and 11 females) with ESRD received carnitine and compared with a matched control group of 30 patients. All the patients had moderate levels of dyslipidemia and were on MHD for at least three months. The dialysis schedule was 4 hour, 2 times a week, using bicarbonate-based dialysate. The patients with hepatic failure or nephrotic syndrome that might affect lipid metabolism and those who had been treated with carnitine or other drugs influencing lipid metabolism, such as β-blockers, glucocorticoids, or lipid lowering agents during the previous eight weeks were excluded from the study. The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences and written informed consent was obtained from all the participants before inclusion.

To measure the lipid profile, blood samples were obtained after a 14-hour fasting and before the hemodialysis sessions. Serum cholesterol and triglycerides were measured by the enzymatic photometric method in the same laboratory. The study patients were prescribed LC tablets 250 mg (Carnitine, SHAHRE DARU,

Tehran, Iran) three times a day for 8 weeks. The routine regimen of hemodialysis was continued during the study period. After two months of treatment, the patients were reevaluated for lipid profile with the same methods and considerations. During the study period, weekly call visits were performed to evaluate any adverse effects of treatment.

### Statistical Analysis

Data are presented as median, mean (standard deviation) or frequency (%), as appropriate. Dyslipidemia was defined as total cholesterol > 200 mg/dL, triglyceride > 150 mg/dL, LDL > 100 mg/dL, or HDL < 35 mg/dL. The values of lipid profile before and after the intervention were compared between the two groups using independent sample *t*-test. Proportions of dyslipidemia before and after the intervention were compared using McNemar test. The mean changes of lipid parameters in the intervention group were compared between men and women with independent sample *t*-test. *P* values of < 0.05 were considered statistically significant.

## Results

The mean age of the patients in our study was 56.7 ± 9.4 years (ranged from 21 to 78 years). The patients were on hemodialysis for 14.9 ± 4.2 months. The mean height and dry weight of the participants were 161 ± 16.3 cm and 63.2 ± 7.3 kg, respectively. Primary renal disease included diabetes mellitus (24 patients), hypertension (8 patients), urologic problems including; obstructive uropathies (8 patients) and adult polycystic kidney disease (4 patients), and unknown etiology (16 patients). No significant drug adverse effects were reported and none of the patients dropped out of the study due to side effects of carnitine.

The mean values of total cholesterol, triglyceride, and LDL-cholesterol significantly decreased after the intervention but the difference for HDL-cholesterol was not statistically significant compared with control group (Table 1). Analyses in patients with low HDL-cholesterol in the intervention group (n = 22) showed that the mean HDL concentration significantly increased after LC supplementation; 28.6 ± 4.6 vs. 30.0 ± 4.6 mg/dL ($P<0.001$). The proportion of patients with low HDL-cholesterol decreased after the study period as well. Expectedly, the proportion of patients with high total cholesterol or hypertriglyceridemia decreased after the intervention period (Table 1). Further analyses showed that the mean decreases in serum concentrations of total cholesterol, triglyceride, and LDL-cholesterol in men were slightly more than women in the intervention group, but the differences were not statistically significant ($P>0.05$).

## Discussion

The results of previous studies on the effect of carnitine supplementation on lipid profile in dialysis patients are conflicting and there is no consensus in this regard. A meta-analysis by Massy et al,[13] on up to 25 trials on carnitine showed that it could decrease cholesterol and triglycerides and increase HDL, but had no effects on LDL and thus carnitine could be considered as a therapeutic option in hemodialysis patients.[13] A systematic review and meta-analysis by Hurot et al,[6] on 482 patients in 18 clinical trials, however, concluded no significant effect of carnitine on triglycerides, total cholesterol, or its fractions. This meta-analysis does not recommend routine carnitine supplementation in hemodialysis patients and suggests performing further studies to clarify the problem. The observed heterogeneity in previous studies could be explained by large variances in sample size, methods of analyses, baseline lipid levels, duration of treatment, and dosage and/or route of administration.[14]

It has been reported that a low dose of intravenous carnitine (<5 mg/kg) significantly improves lipid profile,[15] while a dose of 20 mg/kg intravenously after each session of hemodialysis showed no effect.[16] High levels of carnitine may stimulate fatty acid (and hence triglyceride) synthesis rather than oxidation, which could explain the dose-dependent effects of carnitine. On the other hand, oral carnitine has limited bioavailability, thus higher doses are

required to achieve a therapeutic effect.[17] Comparable to prior reports,[18] our study demonstrated that an oral dose of 750 mg/day (approximately 12 mg/kg) LC significantly improves lipid profile of patients without any significant adverse effects. Noteworthy, it has been reported that patients may tolerate high doses of LC (up to 15 mg/day) with no major side effects,[14] which is in support of our findings.

Who benefits from carnitine supplementation? Plasma and tissue concentrations of carnitine are poorly correlated,[19,20] and carnitine deficiency in muscle might be present in spite of normal plasma levels.[21,22] Thus, it has been suggested that serum carnitine levels may not reliably predict which group of MHD patients benefits from carnitine supplementation. Furthermore, routine tissue measurement is too invasive and expensive. Consequently, further clinical trials are needed to obtain a practical approach in order to define those patients who may benefit from carnitine supplementation.[23] We did not measure carnitine plasma levels, therefore we were not able to evaluate the association of plasma or muscle carnitine levels and efficacy of carnitine supplementation.

Free carnitine levels are known to be increased during the first two months of supplementation and stabilize thereafter, and longer follow-ups may be required to assess the replenished tissue carnitine stores and detect a clinical effect. Accordingly, the short observation period was a limitation for this study.

We conclude that orally administered LC (750 mg/day) is able to improve lipid profile in patients on MHD. Further long-term studies with adequate sample size are needed to define the population of patients who would benefit more from carnitine therapy, and to define the optimal dose and the most efficient route of administration.

## Acknowledgment

The authors appreciate the kind assistance and financial support provided by the Research Chancellor of Isfahan University of Medical Sciences, as well as the colleagues, and the patients who participated in this study.

## References

1. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
2. Ordonez JD, Hiatt RA, Killebrew EJ, Fireman BH. The increased risk of coronary heart disease associated with nephrotic syndrome. Kidney Int 1993;44:638-42.
3. Guarnieri G, Situlin R, Biolo G. Carnitine metabolism in uremia. Am J Kidney Dis 2001;38(4 Suppl 1):S63-7.
4. Hoppel C. The role of carnitine in normal and altered fatty acid metabolism. Am J Kidney Dis 2003;41(4 Suppl 4):S4-12.
5. Bohmer T, Rydning A, Solberg HE. Carnitine levels in human serum in health and disease. Clin Chim Acta 1974;57:55-61.
6. Hurot JM, Cucherat M, Haugh M, Fouque D. Effects of L-carnitine supplementation in maintenance hemodialysis patients: A systematic review. J Am Soc Nephrol 2002;13:708-14.
7. Kletzmayr J, Mayer G, Legenstein E, et al. Anemia and carnitine supplementation in hemodialyzed patients. Kidney Int Suppl 1999; 69:S93-106.
8. Rodriguez-Segade S, Alonso dlP, Paz JM, et al. Carnitine deficiency in haemodialysed patients. Clin Chim Acta 1986;159:249-56.
9. Winchester JF. L-carnitine and peritoneal dialysis. Perit Dial Int 2000;20 Suppl 2:S150-3.
10. Bellinghieri G, Santoro D, Calvani M, Mallamace A, Savica V. Carnitine and hemodialysis. Am J Kidney Dis 2003;41(3 Suppl 1):S116-22.
11. Schreiber B. Levocarnitine and dialysis: A review. Nutr Clin Pract 2005;20:218-43.
12. Guarnieri G, Biolo G, Vinci P, Massolino B, Barazzoni R. Advances in carnitine in chronic uremia. J Ren Nutr 2007;17:23-9.
13. Massy ZA, Ma JZ, Louis TA, Kasiske BL. Lipid-lowering therapy in patients with renal disease. Kidney Int 1995;48:188-98.
14. Goa KL, Brogden RN. l-Carnitine. A preliminary review of its pharmacokinetics, and its therapeutic use in ischaemic cardiac disease and primary and secondary carnitine deficiencies in relationship to its role in fatty acid metabolism. Drugs 1987;34:1-24.
15. Wanner C, Wieland H, Wackerle B, Boeckle H, Schollmeyer P, Horl WH. Ketogenic and

antiketogenic effects of L-carnitine in hemodialysis patients. Kidney Int Suppl 1989;27: S264-8.
16. Golper TA, Wolfson M, Ahmad S, et al. Multicenter trial of L-carnitine in maintenance hemodialysis patients. I. Carnitine concentrations and lipid effects. Kidney Int 1990;38: 904-11.
17. Brass EP. Pharmacokinetic considerations for the therapeutic use of carnitine in hemodialysis patients. Clin Ther 1995;17:176-85.
18. Argani H, Rahbaninoubar M, Ghorbanihagjo A, Golmohammadi Z, Rashtchizadeh N. Effect of L-carnitine on the serum lipoproteins and HDL-C subclasses in hemodialysis patients. Nephron Clin Pract 2005;101:c174-9.
19. Bohmer T, Bergrem H, Eiklid K. Carnitine deficiency induced during intermittent haemodialysis for renal failure. Lancet 1978;1:126-8.
20. Ahmad S. L-carnitine in dialysis patients. Semin Dial 2001;14:209-17.
21. Moorthy AV, Rosenblum M, Rajaram R, Shug AL. A comparison of plasma and muscle carnitine levels in patients on peritoneal or hemodialysis for chronic renal failure. Am J Nephrol 1983;3:205-8.
22. Vacha GM, Corsi M, Giorcelli G, Iddio SD, Maccari F. Serum and muscle L-carnitine levels in hemodialized patients, during and after long-term L-carnitine treatment. Curr Ther Res 1985;37:506-16.
23. Wanner C, Horl WH. Carnitine abnormalities in patients with renal insufficiency. Pathophysiological and therapeutical aspects. Nephron 1988;50:89-102.