Influence of L-Carnitine Supplementation on Serum Lipid Profile in Hemodialysis Patients: A Systematic Review and Meta-Analysis

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Key Words
Hemodialysis • L-Carnitine • Meta-Analysis

Abstract
Background/Aims: An increasing body of evidence demonstrates that L-carnitine plays a pivotal role in lipid metabolism of hemodialysis (HD) patients. However, there are still some reservations about its benefits. Therefore, we performed a meta-analysis to assess the effects of L-carnitine supplementation on lipid profile in HD patients. Methods: Literature search was performed to identify the relevant randomized controlled trials that investigated the effects of L-carnitine on the lipid profile of subjects. Two independent authors used an Excel file to extract data and assess trials quality. The primary effect measure was the difference in means of the final lipid measurements between the intervention and control groups. The meta-analysis was performed with the fixed-effects model or random-effects model according to heterogeneity. Results: Twelve studies with a total of 391 patients met the inclusion criteria. The use of L-carnitine was not associated with a reduction in the total cholesterol (SMD, -0.11; 95% CI, -0.31 to 0.09), HDL-cholesterol (SMD, 0.01; 95% CI, -0.36 to 0.39), VLDL-cholesterol (SMD, 0.54; 95% CI, -0.06 to 1.14), and the serum triglycerides (SMD, -0.12; 95% CI, -0.36 to 0.12). However, L-carnitine can significantly decrease the LDL-cholesterol (SMD, -0.29; 95% CI, -0.53 to -0.06) in HD patients. In a subgroup meta-analysis, a significant LDL-cholesterol-lowering effect of L-carnitine supplementation was observed in intravenous application group, and patients with longer interventional duration and renal diseases. Conclusion: The limited evidence suggests that there was no effect of L-carnitine on serum total cholesterol, HDL-cholesterol, VLDL-cholesterol and serum triglycerides. By contrast, this meta-analysis suggests a promising effect of L-carnitine on LDL-cholesterol. Further large-scale, well-designed randomized controlled trials are urgently needed.
Introduction

Chronic kidney disease (CKD), especially end-stage renal disease (ESRD), is the most frequently health problem and main cause leading to kidney-related deaths. It currently affects approximately 40.3 million adults in 2010, and is projected to reach 54.8 million in 2020 [1]. At present, kidney replacement therapy is the main measure to treat kidney failure, which dramatically improved patients’ survival and the quality of life. It has been reported that a number of factors and co-morbid conditions common in dialysis are implicated as risk factors, including diabetes, hypertension, hyperlipidemia, inflammation, anemia and imbalances in mineral metabolism [2]. Among them, one of the most important complications of cardiovascular origin and the risk of cardiovascular disease in patients with chronic renal disease is hyperlipidemias [3]. It is well known that the concentration of serum lipid is a high burden of patients with dyslipidemia and cardiovascular disease, while cholesterol and triglycerides are objective index for serum lipid, therefore, reduction of cholesterol and triglycerides is important to cut down the overall mortality and mortality in HD patients.

L-carnitine, a small compound, is found mostly in milk and meat. Studies also showed that liver can synthesize the endogenous carnitine from lysine, methionine and ascorbate, niacin, pyridoxine, and Fe^{2+} [4]. L-carnitine plays an important role in the beta-oxidation of fatty acids and can cut down free fatty acid availability for triglyceride synthesis [5, 6]. A number of studies have demonstrated that administration of L-carnitine and its analogues acetyl and propionyl L-carnitine was effective for normalize the concentrations of carnitine, plasma cholesterol, triglycerides in a streptozocin-induced diabetic rat model [7]. Further research has demonstrated that treatment with L-carnitine could prevent the progression of atherosclerotic lesions in hypercholesterolemic rabbit because of its antioxidant and lipid-lowering effects [8]. Recently, a great number of randomized, placebo-controlled studies regarding the effect of L-carnitine supplementation have been reported in patients who undergoing HD. However, these studies have a modest sample size and convey inconclusive results. To better understand the efficacy of L-carnitine supplementation on serum lipid profile in HD patients, we therefore carried out a comprehensive systematic review and meta-analysis of randomized controlled trials to assess the lipid-lowering effects of L-carnitine supplementation in HD patients.

Materials and Methods

Literature search and inclusion criteria

Following the PRISMA statement guidelines for meta-analysis of randomized controlled trials (RCTs) [9], relevant RCTs were identified by searching PubMed and Embase databases (up to July 2013). We also searched The Cochrane Central Register of Controlled Trials (CENTRAL) (also up to July 2013). The structured search strategies used the following format of search terms: ("vitamin BT" OR L-carnitine OR "L carnitine" OR levocarnitine OR bicarnesine OR L-acetylcarnitine OR acetyl-L-carnitine) AND (hemodialysis OR dialysis OR "kidney replacement therapy"). Results were limited to human subjects and English-language publications. The abstracts and meeting proceedings are not included. In addition, we also searched for any additional studies in the reference lists of recent meta-analyses of L-carnitine treatment for HD patients. This process was performed iteratively until no additional articles could be identified.

The full-text publications should be included when the following inclusion criteria were met: (a) study design, RCT reported in a full paper article; (b) study population, adult patients receiving HD; (c) intervention, L-carnitine supplement (no matter what type and regimen applied); (d) comparison intervention, placebo or no intervention; and (e) outcome measure, articles reported ‘baseline’ and ‘end of intervention’ mean and standard deviation values of lipid measurements for the active (intervention) and control groups.

Trials were excluded if they (a) were non-randomized studies or cross-over study design (b) were abstracts, letters, or meeting proceedings; (c) had repeated data, insufficient data or did not report outcomes of interest; and (d) enrolled patients were younger than age 18 years or patients receiving peritoneal dialysis (PD).
Data extraction and quality assessment

Two reviewers (H.H. and L.S.) independently assessed articles for inclusion and tabulated the data from each RCT. The following information was extracted from the eligible studies: first author, year of publication, number of patients (intervention/control), mean age, gender, duration of treatment, types of L-carnitine, regimens of L-carnitine supplementation (dosage, timing), location and time on HD. We also extracted information on the baseline and final concentrations (or net changes) of serum total cholesterol (TC), LDL cholesterol, HDL cholesterol, VLDL cholesterol and triglycerides (TG). Studies that reported results in mmol/l were converted to mg/dl using the standard conversion factors (which was a division of the mmol/l value by 0.02586 for TC, LDL and HDL; and by 0.01129 for TG). Extracted data were entered into a standardized Excel file and were checked by another author (W.Z.). It should be emphasized that if the same population was reported in several publications, we only retained the most informative article or complete study to avoid duplication of information. Discrepancies in the evaluation of some of the studies were resolved through discussion between the authors.

Methodological quality evaluation was independently performed by two of the authors (HHH and LJS) using validated Jadad five-point scale [10]. This tool places emphasis on the following three areas when defining the quality of an RCT: (a) randomization (0-2), (b) double-blinding (0-2), and (c) description of withdrawals and drop-outs (0-1). Jadad scores ranged from 0 to 5, when the scores≤2 indicates the lowest quality and≥3 means the highest quality [11]. Disagreements were resolved through discussion and consensus.

Statistical analysis

All outcome measures were expressed as standardized mean differences (SMDs) with 95% confidence intervals (CIs) using either fixed or random-effects model depending on the amount of heterogeneity. A random-effects model meta-analysis will be conducted for heterogeneous outcomes and a fixed-effect model meta-analysis for homogeneous outcomes. Heterogeneity across studies was tested by using the I^2 statistic (percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error), and the I^2 can be calculated as: \( I^2 = 100 \times \frac{(Q-df)}{Q} \) (\( Q = \text{Cochrane's heterogeneity statistics}, df = \text{degrees of freedom})\). Its ranges between 0 and 100 %. Studies with an I^2 statistic of 25-50 % are considered to have low heterogeneity, those with an I^2 statistic of 50 -75 % are referred to as moderate estimates, and those with an I^2 statistic of > 75 % are referred to as high heterogeneity [12]. Subgroup analysis were planned a priori to determine whether the types of interventions (orally supplementation compared with intravenous application), interventional duration (shorter term compared with longer term), location of subject population (Asian, Europe, and America), or diseases status modified the effect of L-carnitine on lipid profile or explained any heterogeneity seen. We further conducted sensitivity analyses to explore possible explanations for heterogeneity and to examine the influence of various exclusion criteria on the overall pooled estimate. We also investigated the influence of a single study on the overall pooled estimate by omitting one study in each turn. A \( p \) value < 0.05 was judged as statistically significant. We assessed the presence of publication bias by examining funnel plot [13]. All analyses were undertaken using Review Manager (Version 5.1.Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

Results

Study identification and selection

The electronic database (PubMed, Embase, CENTRAL) were searched to identify the potential studies, respectively. A total of 58 citations were obtained by the initial database search. Ten RCTs were excluded because of duplicate studies, and 31 RCTs were excluded after we had reviewed titles and abstracts, mainly because they were reviews, letter, meeting proceedings, or not relevant to our analysis. Moreover, according to the inclusion and exclusion criteria, eight articles were further excluded for the reasons as follows: one study was crossover trial, one study with unavailable data for analysis, and six studies did not report the interest outcomes. Finally, 12 RCTs that met our inclusion criteria were included in the present meta-analysis [14-25], of which three studies were determined through checking reference.
lists of retrieved articles [16-18]. The details of study selection flow were explicitly described in Figure 1.

Characteristics of eligible studies

The main characteristics of the 12 RCTs included in the meta-analysis are summarized in Table 1. These studies were published from 1980 to 2012. A total of 391 patients (209 in the L-carnitine group and 182 in control group) were included in this analysis. All trials included both men and women. Of these 12 included studies, 9 studies compared L-carnitine to placebo [14-21, 25] while 3 studies compared to no treatment [22-24]. The types of interventions were oral or given intravenously. The total dosage of L-carnitine supplementation in the intervention groups ranged from 0.5 to 1g. The treatment duration ranged from 5 weeks to 24 weeks. Among the 12 studies included in the meta-analysis, 7 articles included patients with end-stage renal disease (ESRD) [18-22, 24, 25], 2 included patients with chronically uremic [14, 15], 2 included patients with hyperlipoproteinemia [16, 17] and 1 included patients with renal failure [23]. These include articles are all reported the change of total serum cholesterol, whereas HDL-cholesterol changes were available from 8 reports [15-19, 21, 24, 25], LDL-cholesterol from 8 studies [15-18, 21, 22, 24, 25], and VLDL-cholesterol in only 2 trials [15, 18]. Serum triglycerides variations were analyzed from 10 studies [14-17, 19-22, 24, 25]. We assessed the quality of the included articles using the Jadad quality score, the Jadad score for each article was graded from scores 2 to 5 in this analysis (Table 2). Funnel plots suggested no significant asymmetry in the meta-analyses of TC, LDL-cholesterol, TG and HDL-cholesterol. Thus, there was no publication bias amongst the 12 trials (Figures not shown).

Analysis of the effects of L-carnitine supplementation on total serum cholesterol, HDL-cholesterol, LDL-cholesterol and VLDL-cholesterol

All 12 articles reported the changes of total serum cholesterol in study patients. The aggregated results of these studies suggest that the total serum cholesterol was not significant decreased in the L-carnitine treatment group (SMD, -0.11; 95% CI, -0.31 to 0.09; Figure 2). There was no evidence of heterogeneity for the outcomes (I²=0%). The standardized mean difference (95% CI) of the changes of HDL-cholesterol for patients treated with L-carnitine compared with control was 0.01 (-0.36 to 0.39), which was not statistical significance. (Figure 3). Heterogeneity was noted for this outcome (I²=55%). The effect of L-carnitine on LDL-cholesterol was assessed in 8 trials [15-18, 21, 22, 24, 25]. Based on the results of meta-analysis, the use of L-carnitine can significantly decrease the LDL-cholesterol level (SMD, -0.29; 95% CI, -0.53 to -0.06; Figure 4). Heterogeneity was insignificant for this outcome (I²=0%). Only 2 articles reported the effect of L-carnitine on VLDL-cholesterol level [15, 18], the standardized mean difference (95% CI) of the variations of VLDL-cholesterol for patients treated with L-carnitine compared with control was 0.54 (-0.06 to 1.14), which was
Subgroup analyses according to the types of interventions showed that orally supplementation could not significantly reduce TC, LDL, HDL and TG in participants. Trials of the intravenous application group showed a significant reduction in serum LDL (SMD, -0.31; 95% CI, -0.58 to -0.05), but a non-significant reduction in serum TC, HDL and TG levels. Analysis by diseases status in which study was carried out revealed a significant reduction in serum LDL (SMD, -0.31; 95% CI, -0.57 to -0.05) for the patients with CKD. In addition, Analysis by location in which study was carried out revealed a non-significant reduction in serum TC, LDL, HDL and TG levels in Asia, Europe and America population.

Subsequently, sensitivity analysis was performed by omitting the studies with low quality (Jadad score <3), the pooled results did not change substantially. When we excluded not statistical significance (Figure 5). Minimal heterogeneity was noted for this outcome ($I^2=22\%$).

**Analysis of the effect of L-carnitine supplementation on serum triglycerides**

Ten included studies reported changes in triglycerides [14-17, 19-22, 24, 25], L-carnitine supplementation was not associated with a significant decrease in serum triglycerides level compared with that of controls (SMD, -0.12; 95% CI, -0.36 to 0.12; Figure 6). The test for heterogeneity was insignificant ($I^2=0\%$).

### Table 1. Main Characteristics of included studies

| Study/year | No patients | Mean age (years) | Gender | Duration of HD (weeks) | Intervention (treatment group/control group) |
|------------|-------------|-----------------|--------|-----------------------|---------------------------------------------|
| | | | | | | |
| | | | | | |
Table 2. Quality assessment of the included studies (Jadad score)

| Study or Subgroup       | L-carnitine | Control | Std. Mean Difference | Std. Mean Difference |
|-------------------------|-------------|---------|----------------------|----------------------|
|                         | Mean        | SD      | Total                |                      |
| Study/Year              | Mean        | SD      | Total                | Weight               |
|                         | Mean        | SD      | Total                |                      |
|                         | IV, Fixed   | 95% CI  | IV, Fixed            | 95% CI               |
| Guarnieri /1980         | 146.9       | 31      | 216.3                | 50.3                 | 21                  | 10.7%                | -0.46 [-1.07, 0.16]  |
| Wescuker /1984          | 145.5       | 31.0    | 241.5                | 24.8                 | 27                  | 13.3%                | 0.12 [-0.43, 0.67]   |
| Fagher /1985            | 149.2       | 31.6    | 241.5                | 24.8                 | 27                  | 13.3%                | 0.12 [-0.43, 0.67]   |
| Vesterstreede /1987     | 144.1       | 27.5    | 164.5                | 29.9                 | 11                  | 5.8%                 | -0.69 [-1.52, 0.14]  |
| Labonia /1980           | 149.4       | 31.5    | 241.5                | 24.8                 | 27                  | 13.3%                | 0.12 [-0.43, 0.67]   |
| Rathod /1990            | 149.4       | 31.5    | 241.5                | 24.8                 | 27                  | 13.3%                | 0.12 [-0.43, 0.67]   |
| Shakerki /2000          | 144.1       | 31.5    | 164.5                | 29.9                 | 11                  | 5.8%                 | -0.69 [-1.52, 0.14]  |
| Suchitra /2011          | 149.4       | 31.5    | 241.5                | 24.8                 | 27                  | 13.3%                | 0.12 [-0.43, 0.67]   |
| Vesterstreede /2011     | 149.4       | 31.5    | 241.5                | 24.8                 | 27                  | 13.3%                | 0.12 [-0.43, 0.67]   |
| Total (95% CI)          | 196         | 195     | 100.0%               | -0.11 [-0.31, 0.09]  |

Fig. 2. Forest plot of studies comparing the effect of L-carnitine versus control on total serum cholesterol in HD patients. The sizes of the data markers indicate the weight of each study in the analysis. IV, inverse variance; fixed, fixed effects model. Values are in mg/dl.

Fig. 3. Forest plot of studies comparing the effect of L-carnitine versus control on HDL-cholesterol in HD patients. The sizes of the data markers indicate the weight of each study in the analysis. IV, inverse variance; random, random effects model. Values are in mg/dl.

the two studies (Rathod et al. and Fagher et al.), our findings were similar without great fluctuation (Table 3). Further exclusion were conducted by omitting any single study did not materially alter the overall combined SMD (data not shown), which adds robustness to our main finding.
Discussion

This is a further systematic review and meta-analysis to evaluate the effects of L-carnitine supplementation on the serum lipid level. The present meta-analysis of 12 randomized controlled trials showed that L-carnitine supplementation was not associated with a significant decrease in total serum cholesterol, HDL-cholesterol, VLDL-cholesterol and serum triglycerides level. However, L-carnitine supplementation could significantly decrease the LDL-cholesterol level in HD patients.
A previous meta-analysis conducted by Hurot et al. [26] showed that L-carnitine supplementation did not result in a significant decrease in total serum cholesterol, HDL-cholesterol, VLDL-cholesterol, and serum triglycerides level, which is in consistent with the previous meta-analysis [26]. However, our study demonstrated that L-carnitine supplementation could significantly decrease the LDL-cholesterol level, which indicates L-carnitine supplementation may be useful for LDL-cholesterol reduction in HD patients. Finally, sensitivity analysis was conducted by omitting any single trial or based on various exclusion criteria, but it did not materially alter the pooled results, which adds robustness to our main point.
There was moderate heterogeneity between studies in the overall analysis of HDL-cholesterol, which may be due to different characteristics of the populations, L-carnitine supplementation, and study designs. Our sensitivity analysis suggests that two trials conducted by Rathod et al. [21] and Fagher et al. [16] probably contributed to the heterogeneity. For some patients included in this trial [21] were allowed to use furosemide or iron supplements during the study. A number of studies have demonstrated that use of furosemide may increase the triglycerides and decrease HDL-cholesterol [27, 28]. Iron was reported to promote the synthesis of HDL and accelerate the process of membrane lipid peroxidation in vitro [29, 30]. In another trial conducted by Fagher et al. [16], we found that some patients enrolled were smokers and this habit remained unchanged during the study. Therefore, these factors may potentially impact on our results and result in the heterogeneity. After omitting both two studies, L-carnitine supplementation was associated with a significant reduce in LDL-cholesterol level (SMD, -0.33; 95%CI, -0.58 to -0.07), while was not associated with the reduction of TC, HDL and TG levels. Further exclusion of any single article of the included studies, it did not materially alter the overall combined SMD.

The principle finding of our meta-analysis seems to contradict the aforementioned studies on the effects of L-carnitine supplementations on the LDL-cholesterol level. It has been reported that LDL-cholesterol is a risk factor in cardiovascular disease, especially in Coronary Atherosclerotic (AS) [31, 32]. Plasma levels of small, dense low-density lipoprotein (LDL) were reported to be increased in chronic kidney disease patients who undergoing HD [33, 34]. Our meta-analysis revealed that the use of L-carnitine may decrease the LDL-cholesterol level in HD patients, which provide a useful information for clinical practice. Moreover, the significant lipid-lowering effects between L-carnitine and LDL-cholesterol appeared to be confined to intravenous application, longer term interventional duration and CKD populations in the subgroup analyses. However, it should be noted that these results are not conclusive and further adequately powered studies are needed. Further studies should pay more attention to this clinical endpoint, so more high-quality randomized clinical trials are warranted.

There were several limitations in our meta-analysis. Firstly, because of the inability to fully adjust for various confounders, the beneficial effect of L-carnitine supplementation on HD patients could be attributed to other healthy habits, such as high fruit and fish consumption. At the same time, some bad habits (eg. smoking and drinking) could also impact on our results. Secondly, owing to different methods used to assess and report L-carnitine supplementation across studies, we failed to evaluate a dose-response relation between L-carnitine supplementation and lipid-lowering effects. Thirdly, although clear inclusion and exclusion criteria were made, significant differences still existed among study design, time on HD, and patient’s daily diet. These factors may have a potential impact on our results. Finally, the analysis was only based on published data and unpublished data were not included.

Further studies should focus on the following points. There is a need to standardize a L-carnitine protocol (such as consistency regarding dosage, route, timing, and duration of administration) since great variability exists in the literature. In addition, the synergistic effects of other coexisting substances and L-carnitine on the clinical outcomes of HD patients need to be excluded. Finally, evidence from the current study indicated that L-carnitine are generally considered effective and well tolerated, but future studies should also pay more attention to the side effects of L-carnitine.

Conclusions

In conclusion, based on current best evidence, our meta-analysis revealed that L-carnitine supplementation was associated with reduction of LDL-cholesterol level, although it was not associated with a significant decrease in total serum cholesterol, HDL-cholesterol, VLDL-
cholesterol and serum triglycerides level. However, relevant evidence is still limited but is accumulating. Thus, further large-scale, well-designed RCTs are urgently needed.

Conflict of Interests

The authors have no conflicts of interest to disclose.

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