Effects of L-Carnitine Supplementation in Maintenance Hemodialysis Patients: A Systematic Review

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Abstract. There are many causes for carnitine depletion during maintenance hemodialysis. Supplementation with L-carnitine in animals has been associated with improvement in some abnormalities also present in chronic renal failure. However, it is still controversial whether restoring plasma or tissue carnitine will correct clinical or biologic symptoms observed in maintenance hemodialysis. A systematic review is here performed to determine the effects of L-carnitine in maintenance hemodialysis patients. Eighty-three prospective trials were identified from 1978 to 1999 in which L-carnitine was randomly allocated in 21 trials. Change in serum triglycerides, cholesterol fractions, hemoglobin levels, erythropoietin dose, and other symptoms (muscle function, exercise capacity, and quality of life) were examined. A total of 482 patients in 18 trials were considered for analysis. There was no effect of L-carnitine on triglycerides, total cholesterol, or any of its fractions. Before the erythropoietin (EPO) era, L-carnitine treatment was associated with improved hemoglobin (P < 0.01) and with a decreased EPO dose (P < 0.01) and improved resistance to EPO when patients routinely received EPO. Muscle function, exercise capacity, and quality of life could not be reliably assessed because of the noncombinable nature of end points and the limited number of trials. In conclusion, L-carnitine cannot be recommended for treating the dyslipidemia of maintenance hemodialysis patients. By contrast, this review suggests a promising effect of L-carnitine on anemia management. The route of L-carnitine administration should be evaluated because there is no evidence as to the most efficient method of administration in maintenance hemodialysis.

L-carnitine is a small compound (molecular weight, 162 D) found mostly in milk and meat. The liver also represents one of the main sources of endogenous carnitine synthesis from lysine, methionine and ascorbate, niacin, pyridoxine, and Fe²⁺ (25). Carnitine is captured and stored by the muscle because there is no carnitine synthesis in muscle. Carnitine is metabolized for numerous metabolic purposes, and among these, the most critical are the regulation of ketogenesis (26), adaptation of mitochondrial energy control, free fatty acid (FFA) transport, and clearance (27). Regulation of FFA β-oxidation occurs through an adaptation of the FFA mitochondrial content from an exit of acyl and acetyl moieties, thus modifying the esterified carnitine (EC)/free carnitine (FC) ratio. The carnitine shuttle allows an adequate mitochondrial FFA content and protects against a downregulation of β-oxidation observed in certain conditions such as metabolic acidosis, hypoxemia, or impaired glucose metabolism.

During chronic renal failure and before maintenance hemodialysis, total carnitine accumulates in response to a decreased renal clearance of EC moieties (28). Furthermore, there is an increased need for FC in response to hypoxemia or acidosis. By contrast, patients undergoing maintenance hemodialysis not uncommonly present with serum carnitine deficiency (29). Indeed, serum carnitine rapidly decreases to 40% of baseline level during the dialysis session (12,30). It is more difficult to assess muscle carnitine for technical reasons and because of a great variability of muscle carnitine in healthy volunteers. In addition, biopsies have been performed at nonstandardized time points from the beginning of the dialysis session, preventing any comparison between studies (31,32). The role of dialysis membranes on carnitine loss into the dialysate is also uncertain. It should be emphasized, however, that carnitine cofactors and precursors may be lost throughout the dialysis session (e.g., vitamin B6, niacin, vitamin C, lysine, and methionine). Due to a molecular weight gradient, the EC moieties are less likely to be filtered by the membrane than the FC, further impairing the abnormal serum EC/FC ratio already present before end-stage renal disease.

The potential targets for administering L-carnitine in maintenance hemodialysis patients include: (1) dyslipidemia, because carnitine increases mitochondrial transport of FFA and reduces FFA availability for triglycerides synthesis; (2) muscle weakness, because of a decreased muscle carnitine content; (3) cardiac symptoms, because the myocyte has one of the highest intracellular carnitine concentrations of the body and myocardial ischemia generates acylcarnitine products and intracellular lactate production; and (4) anemia for correcting numerous
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<td>17</td>
<td>8</td>
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<td>Labonia</td>
<td>1995</td>
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<td>1998</td>
<td>21</td>
<td>—</td>
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<td>PO</td>
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<td>1999</td>
<td>22</td>
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<td>4 mo</td>
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<td>Altmann et al.</td>
<td>1999</td>
<td>23 (abstract)</td>
<td>15</td>
<td>15</td>
<td>IV</td>
<td>20 mg/kg</td>
<td>16 wk</td>
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<tr>
<td>Mitwalli et al.</td>
<td>1999</td>
<td>24 (abstract)</td>
<td>18</td>
<td>13</td>
<td>IV</td>
<td>15 mg/kg</td>
<td>6 mo</td>
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a IV, intravenous during hemodialysis; PO, per os/day; ID, into the hemodialysate.

b First arm before crossover.

c 1-carnitine added to the dialysate at the final concentration of 100 μmol/L.

d Study report prevents the identification of patient n in each subgroup (total = 101 patients).

Number of patients may vary according to analyzed parameter (see Figures).
metabolic abnormalities (e.g., oxidative stress and impaired phospholipid turnover). A number of experimental studies have shown that administering L-carnitine to depleted animals has potential benefits for myocardial function, muscle composition, and other various parameters. Since 1978, many trials have been conducted in human to evaluate the effects of administering L-carnitine. Despite the fact that nearly 2000 patients were included in more than 80 studies, it is still a matter of debate as to whether L-carnitine treatment can improve patient’s status and symptoms. We therefore conducted a systematic review on the effects of L-carnitine treatment in adult maintenance hemodialysis patients.

Materials and Methods

**Trial Retrieval and Selection Processes**

The trial search strategy was developed specifically for checking electronic databases (MEDLINE, Embase, LILACS, Cochrane Library) for clinical trials assessing the effects of L-carnitine supplementation in adult maintenance dialysis patients. We also searched the renal trials register of clinical trials, which was developed in-house through the Cochrane Collaboration handsearching program. We had direct contacts with Sigma-Tau Laboratory, Italy, who kindly provided additional references of clinical trials addressing the L-carnitine treatment issue. Articles not written in English, French, Italian, or Spanish language were translated into English. Authors of abstracts were contacted if the reported data were not sufficient for analysis. Inclusion criteria were as follows: random allocation of treatment, control group receiving a placebo or no treatment, clinical outcome, or laboratory parameters relevant to end-stage renal disease condition. Crossover trials were also included if the order for administering L-carnitine was randomly chosen at the start of the study and the data for the first crossover period only was available. Nonrandomized trials, e.g., controlled clinical trials in which the treatment was not randomly allocated, prospective uncontrolled trials, and retrospective trials were excluded from analysis (see Table 1 for selected trials). The study quality was systematically assessed in an open fashion at the time of data collection.

**Statistical Analyses**

Data were pooled using the Hedges and Olkin method designed for quantitative data (33). To allow their pooling, the results of each study were converted into an effect size (standardized difference). Providing heterogeneity was not present, the data were pooled according to a simple fixed-effect model. An overall treatment effect size was calculated as the average of the result of each study weighted to the inverse of its variance (corresponding to a fixed effect model). If heterogeneity was detected (at a level of significance of $P < 0.10$), a random effect model was used (33). All statistics used two-tailed tests, with a threshold of statistical significance of $P \leq 0.01$.

**Results**

From January 1978 to April 1999, a total number of 620 references, including “carnitine in title AND patients,” were retrieved. From these, we identified 163 papers addressing the renal failure condition. There was no provision of L-carnitine to patients in 84 of them. L-carnitine was therefore administered to patients in 79 published studies, of which 62 were not controlled (list available on request). Thus, only 17 published trials addressed the effects of L-carnitine in a random and controlled manner (Table 1). We were able to identify four subsequent abstracts of studies also including a random administration of L-carnitine (Table 1). We then excluded from analysis three randomized trials (Mitwalli et al., 1999; Sloan et al., 1998; Trivelli et al., 1982, Table 1) because data available in these papers or after contacting the investigators were not suitable for analysis of selected criteria (data relevant to our analysis not recorded during trial for one, no response after contacting authors for one, and quality of life estimation only for one). Finally, we analyzed data obtained from 18 trials and 482 patients (mean, 27 patients per study; range, 10 to 82).

**Effects of L-Carnitine Treatment on Serum Lipid Profile**

As seen in Figures 1 and 2, the effects of L-carnitine on serum lipid profiles were variable, and no clear conclusions can be drawn from the individual studies. Serum triglycerides variations were compared between patients receiving L-carnitine and those not receiving L-carnitine in nine trials (Figure 1). Five trials showed nonsignificant serum triglycerides changes, whereas four reported significant variations between treated and control patients, two being in favor of L-carnitine supplementation and two against L-carnitine. It should be noted that the size of these trials was probably too small to provide a sufficient statistical power. Despite improving statistical power by increasing the patient number to 250, no statistically significant change in serum triglycerides profile was observed. The meta-analysis showed an overall effect size of 0.11, which suggests a nonsignificant increase in serum triglycerides ($P = 0.81; n = 250$). The carnitine effect was heterogeneous between studies, and this was still present after the use of a random effect model ($P$ heterogeneity $< 0.01$; e.g., Cochran Q test on Figure 1[H]).

The changes in serum cholesterol fractions were analyzed
from nine studies. Total serum cholesterol variations were obtained in all nine studies (Figure 1), whereas HDL-cholesterol changes were available from eight studies, LDL-cholesterol from five studies, and VLDL-cholesterol in only three trials (Figure 2). Again, there was no significant change in any of the individual trials. The overall changes obtained by pooling the data were not statistically significant for serum total cholesterol or for any of its fractions (Figures 1 and 2). No heterogeneity was observed ($P$ heterogeneity $> 0.1$; Figures 1 and 2).

**Effects of L-Carnitine Treatment on Anemia and Erythropoietin Requirement**

Before the introduction of recombinant human erythropoietin (EPO), some studies assessed the effects of L-carnitine on patients’ hemoglobin or hematocrit levels. The hemoglobin levels increased in the groups receiving l-carnitine as compared with the groups not receiving L-carnitine (Figure 3). When pooled, these three studies resulted in a statistically significant common size effect of 0.50 ($P < 0.01$; Figure 3). This size effect indicates that a patient in the 50th percentile of hemoglobin level distribution in the placebo group would reach the 70th percentile if treated by L-carnitine. Although this does not indicate a 20% increase in hemoglobin level, this improvement is clinically significant. No statistically significant heterogeneity was detected ($P$ heterogeneity $= 0.20$; Figure 3).

Recombinant human EPO became available in 1989. We identified six randomized trials addressing the question of whether it was possible, by providing L-carnitine, to reduce the EPO dose while maintaining a constant hemoglobin or hematocrit level (Figure 3). A reduction in EPO dose was achieved in the carnitine-treated groups in five of the six studies while maintaining a comparable target hemoglobin in both the carnitine and control groups. The EPO dose was significantly smaller as compared with the control groups in four trials (Figure 3). A common effect size of −0.75 (random effect model) was observed, with a statistically significant level of heterogeneity ($P$ heterogeneity $= 0.02$). This indicates that a patient in the 50th percentile of EPO dose distribution in the placebo group would reduce his/her EPO dose to the 23rd percentile if treated by L-carnitine. The effects of L-carnitine supplements between trials were, however, heterogeneous; therefore, the conclusion appears less robust.

Figure 4 shows the EPO resistance index (ERI), as defined by the EPO dose given per gram of hemoglobin to maintain a constant hemoglobin (or hematocrit) level. We were
able to calculate this index in four trials only. In the control groups, there was no change in EPO dose and no variation in hemoglobin levels, resulting in an unmodified ERI (Figure 4, left). By contrast, in the carnitine-treated groups, the ERI decreased in three of the four studies, in favor of an improvement in this index (Figure 4, right).

**Effects of L-Carnitine Treatment on Myocardial Function, Arrhythmia, Asthenia, and Exercise Capacity**

Other frequent symptoms related to maintenance dialysis have also been examined as potential targets for L-carnitine adjuvant treatment: myocardial function (7,17), arrhythmia (17), asthenia and fatigue (4,13,15), exercise capacity, and muscle weakness (1,9,13,14). However, after careful analysis of individual trials, data were not combinable because most of these trials used heterogeneous design or assessment methods that have been poorly or not validated in dialysis patients.

**Discussion**

There are compelling indicators of carnitine loss and/or deficiency in maintenance dialysis patients as a result of low dietary intakes and increased losses during the dialysis procedure (29,35). However, restoring serum or tissue carnitine levels may not be sufficient to correct the patients’ symptoms; therefore, the efficacy of L-carnitine administration should be assessed through good quality clinical trials with adequate clinical outcome measures. The present results are from an exploratory meta-analysis, because no specific hypothesis was defined before analysis. Therefore, the results can only suggest treatment effects but not demonstrate them. Other general limitations are the overall small number of patients in the individual trials and the limited number of double blind designed studies, leaving a potential investigator bias (Table 1). Other types of biases may have occurred that should be discussed. Publication bias, which is the consequence of negative studies rejected for publication, may reinforce the weight of positive published studies (36,37). We did not observe for any parameter analyzed a more important weight of studies that included a larger number of patients, which may have a greater chance to be published. The fact that we chose to analyze only randomized trials, although leading to a dramatic reduction in trials selection, protects against a well-described artificial increase in treatment effect estimate in response to investigators biases and bad quality clinical trials (38). Finally, language bias may have been reduced by including trials in Italian and Korean language and searching LILACS, the South American Spanish clinical trial database.

We were not able to find any significant effect of L-carnitine supplementation on serum lipid profile in maintenance dialysis patients. The effect of L-carnitine on triglycerides was heterogeneous in the nine trials included (Figure 1), whereas the effects on total cholesterol (Figure 1) or its fraction (Figure 2) were not heterogeneous, despite a smaller number of trials. This heterogeneity could be explained by differences in baseline levels of triglycerides, dose-ranging effects, or center or population effects. Opposite to the expectation, there was a trend for an overall increase in serum triglycerides, even though the results were not statistically significant (Figure 1). The risk difference observed for the LDL cholesterol fraction provided a P value of 0.06 (Figure 2) but was not considered significant because of the exploratory approach and multiple comparison tests with an increased risk of type I error. To further clarify this point, we suggest that an additional adequately sized trial should be performed. To date however, these results suggest that L-carnitine supplementation may not be efficacious for controlling the renal failure-induced dyslipidemia, particularly when compared with other currently approved medications.

Before erythropoietin (EPO) became available in 1989, the fact that L-carnitine administration could improve the patients’ anemia status was already noticed (39). In the present review, we identified three randomized controlled trials performed in the pre-EPO era, of which two showed a statistically significant favorable effect of L-carnitine supplement on hemoglobin level (Figure 3), although these trials included only a low number of patients (Table 1). After 1989, the favorable effect of L-carnitine on red cells were confirmed by analyzing randomized trials in which L-carnitine was administered concomitantly with EPO (Figure 3). In these more recent studies, the purpose was to maintain a comparable hemoglobin or hematocrit level in both groups by progressively reducing the EPO dose in the carnitine group. We used the erythropoietin resistance index (ERI) to express the body response to L-carnitine, i.e., the ratio of the EPO dose divided by the patient’s hemoglobin level. Any increase in hemoglobin or decrease in EPO dose during the study would induce a reduction in this index. Figure 4 expresses the percent decrease in ERI in both groups available in four trials. This index was reduced by L-carnitine supplement (Figure 4, right), suggesting that L-carnitine improves erythropoietin efficiency as compared with control groups (Figure 4, left). Together with the previous observation of improved anemia before the EPO era (Figure 3), these findings suggest a beneficial effect of L-carnitine supplement on anemia control in maintenance hemodialysis patients. Whether those effects are constant in all patients should be further explored. Indeed, Caruso et al. (20) showed no overall
effect of L-carnitine on hemoglobin level after 6 mo of treatment in their entire population, but patients older than 65 yr receiving carnitine needed a lower EPO dose to maintain their hematocrit level 3 mo after the end of trial, compared with elderly patients not receiving L-carnitine (20). Finally, we were not able to find a dose-response pattern, and we did not observe a time lag for this beneficial effect. However, the number of patients was limited, and larger studies will be needed to clarify this important clinical point.

In this meta-analysis, we were not able to reliably assess the effects of L-carnitine treatment on exercise capacity or cardiovascular instability, because there was a large heterogeneity for defining and recording these clinical symptoms, preventing any pooling of data. Some trials used V02 max while others used a subjective assessment with different scales, most of which have not been validated for use in chronic renal failure patients. Information should therefore be obtained from future good quality, well-designed trials.

The results of this meta-analysis justify a new randomized controlled trial to evaluate the utility of adjuvant L-carnitine treatment for anemia management in hemodialysis patients (40). On the basis of this meta-analysis, 260 patients should be enrolled to reach the statistical power to observe a reduction of 20% in the EPO dose from a weekly dose of 6000 ± 3000 IU. Cost-benefit analysis should include the estimation of money spared by the achieved reduction in EPO dose and the additional L-carnitine expenses. The route of administration of L-carnitine should also be assessed because there is no evidence from clinical trials as to the most efficient method of L-carnitine administration in maintenance hemodialysis patients.

References