International Urology and Nephrology
https://doi.org/10.1007/s11255-021-02835-5

NEPHROLOGY - ORIGINAL PAPER

Effect of L-carnitine supplementation on renal anemia in patients on hemodialysis: a meta-analysis

Yan Zhu[1,2] · Chao Xue[2] · Jihong Ou[1] · Zhijuan Xie[1] · Jin Deng[1]

Received: 19 December 2020 / Accepted: 6 March 2021
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Abstract

Background L-carnitine is an amino acid derivative that is thought to be helpful for treating renal anemia in hemodialysis patients. However, the mechanism remains to be fully elucidated.

Methods A literature search was performed on PubMed, Embase, and Cochrane Central Register of Controlled Trials to identify randomized controlled trials (RCTs) and conduct a meta-analysis for investigating the effect of L-carnitine in the treatment of renal anemia in participants receiving hemodialysis.

Results A total of 18 eligible trials with 1090 participants were included in this study. L-carnitine can significantly increase plasma free L-carnitine levels (mean difference [MD]: 140.53, 95% confidence interval [CI] 102.22–178.85; $P < 0.00001$), decrease the erythropoietin responsiveness index (ERI; MD: −2.72, 95% CI −3.20 to −2.24; $P < 0.00001$) and the required erythropoiesis–stimulating agent (ESA) doses (MD: −1.70, 95% CI −2.04 to −1.36; $P < 0.00001$). However, the use of L-carnitine was not associated with a higher hemoglobin level (MD: 0.18, 95% CI −0.20 to 0.55; $P = 0.35$) and hematocrit level (MD: 1.07, 95% CI −0.73 to 2.87; $P = 0.24$). In subgroup analyses, the effects of L-carnitine supplementation on renal anemia in patients on hemodialysis were independent of the treatment duration and intervention routes.

Conclusion The present meta-analysis indicated that L-carnitine therapy significantly increased plasma L-carnitine concentrations, improved the response to ESA, decreased the required ESA doses in patients receiving hemodialysis, and maintained hemoglobin and hematocrit levels. L-carnitine supplementation should be supported in hemodialysis patients. However, the relationship between L-carnitine treatment and long-term outcomes is still unclear. Further high-quality RCTs are needed to verify our findings.

Keywords L-Carnitine · Hemodialysis · Erythropoietin responsiveness index · Erythropoiesis-stimulating agent · Renal anemia

Introduction

Renal anemia, a commonly observed complication in patients with chronic kidney disease (CKD), is associated with increased mortality and cardiac complications and contributes to poor quality of life [1]. Although the etiology of anemia in CKD is driven by iron deficiency, decreased half-life of erythrocytes and chronic inflammation, the main pathogenesis is still erythropoietin (EPO) deficiency [2]. Randomized controlled trials (RCTs) have proved that erythropoiesis-stimulating agent (ESA) can increase hemoglobin levels, which prompted the widespread use of ESA to correct anemia [3]. However, treatment with higher doses of ESAs is related to an increased risk of death and cardiovascular events in patients with CKD [4, 5]. In addition, ESA hyporesponsiveness results in failure of improving hemoglobin levels in a considerable number of patients, even at high doses of ESA and also influences renal anemia [6]. Therefore, it is necessary to minimize the use of ESA and improve the response to ESA.

L-carnitine is an amino acid derivative that exists in almost all animal species, some microorganisms, and several higher plants. It is biosynthesized mainly in the liver and kidneys, and more than 90% of L-carnitine is present within the skeletal and cardiac muscles [7]. The main function of

✉ Yan Zhu
zymonica@126.com

1 Department of Nephrology, The First Affiliated Hospital of University of South China, Hengyang, China

2 Department of Nephrology, The Second Affiliated Hospital of Guangxi Medical University, Nanning, China

Published online: 13 March 2021

L-carnitine in the organism is to transport long-chain fatty acids into the mitochondrial matrix for β-oxidation and tricarboxylic acid cycle to produce ATP for energy supply [8]. Under normal renal functions, L-carnitine is filtered in the glomerulus and resorbed in the proximal tubules to maintain L-carnitine homeostasis in the body. However, patients with chronic renal failure, especially those receiving hemodialysis, suffer from L-carnitine deficiency due to reduced intake or rapid clearance during dialysis, thereby resulting in several symptoms such as anemia, dialysis hypotension, myocardial damage, and malnutrition [8, 9]. Several RCTs showed that L-carnitine supplementation can improve RBC survival [10], leading to a reduction in ESAs usage and improving ESAs hyporesponsive [11]. However, other studies have conflicting results [12]. Therefore, we conducted a meta-analysis to pool the data of ESAs dose and erythropoietin responsiveness index (ERI) to evaluate the efficacy of L-carnitine in the treatment of renal anemia in hemodialysis patients.

Methods

Literature search

Two authors (Y Zhu and ZJ Xie) independently conducted literature searches in PubMed, Embase, and Cochrane Central Register of Controlled Trials in October, 2020. The following search terms were used: "carnitine OR L-carnitine OR levocarnitine" and "dialysis OR hemodialysis." The references included in the literature and all relevant review articles were reviewed to supplement possible missing studies. Only English and Chinese language trials were included to consider for the selection of RCTs.

Inclusion criteria and prespecified outcomes

The inclusion criteria were as follows: (1) participants aged ≥18 years; (2) parallel and crossover RCTs that compared L-carnitine supplementation with placebo or no treatment; (3) a diagnosis with ESRD receiving hemodialysis treatment for a period of at least 12 weeks; (4) the participants underwent regular 4-h hemodialysis sessions twice or thrice weekly. Studies that conducted oral or intravenous L-carnitine supplementation within the past 6 months and those that performed L-carnitine supplementation for less than 1 month were excluded.

The primary outcome was ERI. Secondary outcomes were the required ESA doses, serum hemoglobin, serum hematocrit, serum free L-carnitine level, and adverse events of L-carnitine supplementation. The ERI was calculated as follows: ERI = ESA doses per week (IU)/Body weight (kg) ◇Hemoglobin level (mg/dL).

Study selection and data extraction

The initial evaluation was screened by two reviewers (Y Zhu and J Deng) independently according to titles and abstracts. Full-text reading was conducted if the studies were not excluded after the initial evaluation. Disagreements were resolved by consultation with a third reviewer. The information extracted from each trial included the first author, year of publication, patient baseline characteristics (country, age, sex, duration of hemodialysis), intervention routes, doses, duration, baseline serum hemoglobin and free L-carnitine levels, outcomes, and the study design.

Quality assessment methods

The Cochrane Risk of Bias Tool was used to assess the quality of studies. Seven elements including a random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and any other potential biases, were judged as high, low, or unclear risk of bias.

Statistical analysis

Continuous data were computed as the mean difference (MD) with 95% confidence interval (CI). Statistical heterogeneity was explored using the I^2 statistic. I^2 statistics of 25–50%, 50–75%, and >75% indicated mild, moderate, and considerable heterogeneity, respectively. If I^2 was <50%, a fixed-effect model was used; otherwise, a random-effect model was used for the analysis. $P < 0.05$ in the two-tailed tests was considered statistically significant. Furthermore, the potential sources of heterogeneity were explored using subgroup analysis, which was performed to assess whether the pooled outcomes were different as a result of the duration of L-carnitine treatment (< 6 or ≧6 months) and the route of L-carnitine treatment (intravenous or oral). Sensitivity analysis was carried out by removing trials one by one and performed again whether the results were different. Publication bias was explored using funnel plots for the primary outcome. Review Manage version 5.3 (Oxford, UK) and STATA 15.1 software were used for the statistical analyses.

Results

Literature selection and baseline characteristics of the participants

We identified 1341 literatures, 1252 of which were excluded after we screened the titles and abstracts. Then, 71 literatures

were excluded after full-text screening as they were not RCTs, used other intervention methods, and did not have appropriate control or failed to meet the inclusion criteria. A total of 18 eligible trials with 1090 participants were included in this meta-analysis: 17 parallel RCTs [10, 11, 13–27] and 1 crossover RCT [28] (Fig. 1). The main characteristics of the participants and the interventions used in the included studies are summarized in Table 1. The number of participants enrolled in this meta-analysis ranged from 17 to 326. Within each study, the percentage of male participants varied between 31 and 100%, and the mean age of participants ranged from 40.3 years to 70 years. Most of the participants (67%) had a hemoglobin level more than 10 g/dL, and nearly all of them presented L-carnitine deficiency (serum free L-carnitine < 40 μmol/L) [25]. Eleven studies compared L-carnitine with matched placebo, and seven studies compared L-carnitine with conventional treatment (only EPO and/or iron supplementation). The duration of L-carnitine supplementation was <6 months in six trials and ≧6 months in 13 trials. L-carnitine was administered intravenously in 15 trials, and orally administered in the 3 remaining trials.

Study quality and publication bias

Figure 2 represented the quality assessment for the included studies. Random sequence generation was described adequately in all studies. However, 11 studies did not report the allocation concealment clearly. Double-blind design was used in eight studies, whereas single-blind conditions were employed in two studies. The results pooled in this meta-analysis were all laboratory measures, which were less likely to be affected by a non-blind design. The ESA doses were used to evaluate publication bias, and no evidence of publication bias was observed in the included studies (Fig. 3).

Effect of L-carnitine on erythrocyte responsive index

Seven studies with 533 participants described the ERI information between the L-carnitine group and the control group. The duration of L-carnitine treatment was more than 6 months. Compared with the control group, a significant reduction in ERI was observed in the L-carnitine group (MD = −2.72, 95% CI −3.20 to −2.24; $P < 0.00001$; $I^2 = 0\%$; Fig. 4), and the fixed-effect model was used. Subgroup analyses showed that no difference in ERI reduction between oral administration (MD = −2.18, 95% CI −3.21 to −1.16, $P < 0.0001$) and intravenous administration (MD = −2.88, 95% CI −3.42 to −2.33, $P < 0.00001$) in ERI reduction (Table 2).

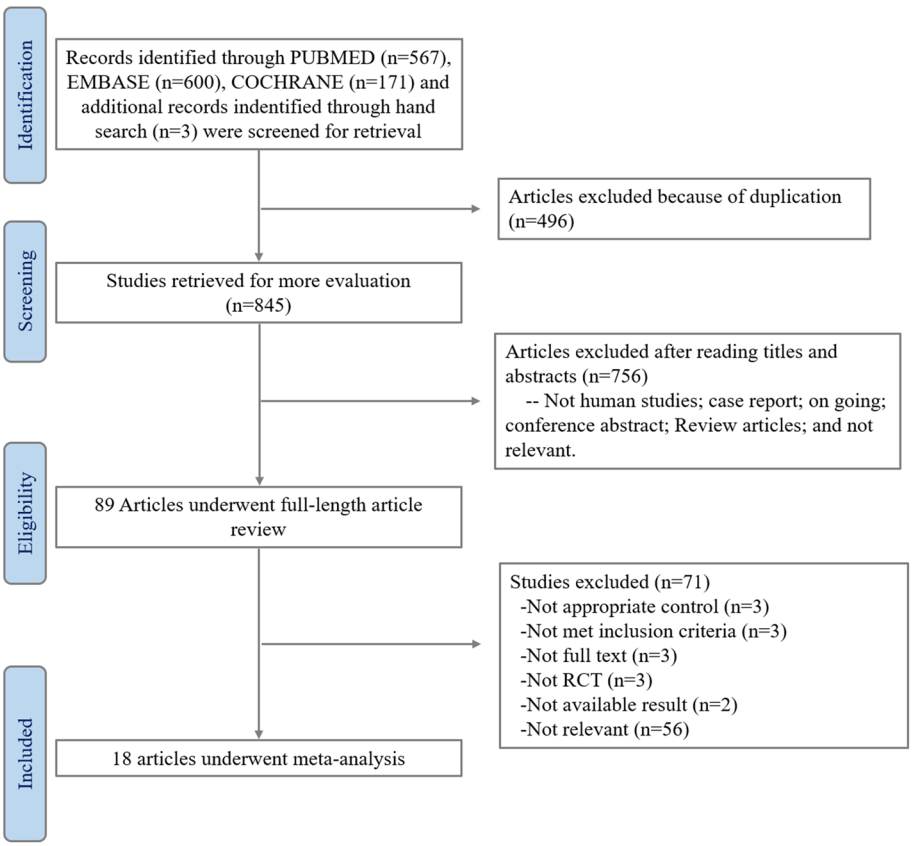

Fig. 1 Literature search flow diagram

Table 1 Characteristics of the included studies in the meta-analysis ($n = 19$)

Study	Country	Design	Age (y)	Patients *n* (% of male)	Route	Control	Baseline Hb or Hct level (g/dL)	Baseline free L-carnitine (μmol/L)	Doses	Outcomes[b]
Alattiya 2016 [13]	Japan	RCT	L: 67 ± 11 C: 68 ± 10	L: 88 (74) C: 88 (72)	Oral	No therapy	L: 10.9 ± 0.9 C: 10.9 ± 0.9	L: 26.7 ± 7.6 C: 23.9 ± 6.3	140 mg/kg/week (12 months)	Hb→, ERI↓
Arduini 2006 [10]	UK	RCT	Not mention	Not mention	IV[a]	Placebo	L: 11.1 ± 1.4 C: 11.1 ± 1	LC deficiency	60 mg/kg/week (6 months)	Hb↑, Hct↑
Brass 2001 [14]	US	RCT	L_A: 42 (19–76) C_A: 45 (23–64) L_B: 47 (25–79) C_B: 43 (24–67)	L_A: 28 (57) C_A: 28 (57) L_B: 94 (70) C_B: 33(61)	IV	Placebo	L_A: 11.3 ± 1.2 C_A: 11.0 ± 1.0 L_B: 11.2 ± 1.1 C_B: 11.4 ± 1.0	L_A: 27.1 ± 6.4 C_A: 23.7 ± 8.9 L_B: 23.9 ± 8.8 C_B: 24.4 ± 8.7	A: 60 mg/kg/week B: 30, 60, 120 mg/kg/week (24 weeks)	Hb→, Hct→
Chazot 2003 [15]	France	RCT	L: 66.7 (40.6–88.0) C: 65.5 (37.5–87.9)	L: 23 (61) C: 22 (50)	IV	No therapy	L_{Hct}: 35.2 ± 7.3 C_{Hct}: 33.1 ± 5.9	L: 22.7 ± 9.0 C: 24.0 ± 9.9	45 mg/kg/week (6 months)	ESA doses→, Hct→
Cui 2016 [16]	China	RCT	L: 50 ± 10 C: 49 ± 10	L: 78 (54) C: 78 (51)	IV	No therapy	L: 7.49 ± 1.43 C: 7.53 ± 1.49	– –	2.0–3.0 g/weeks (28 weeks)	ESA doses↓, Hb↑, Hct↑
Emami 2012 [17]	Iran	RCT	L: 53.9 ± 17.2 C: 51.8 ± 13.5	L: 24 (50) C: 27 (52)	Oral	Placebo	L: 10.5 ± 2.5 C: 9.5 ± 2.2	– –	7.0 g/weeks (16 weeks)	ESA doses↓, Hb→
Fu 2010 [18]	China	RCT	53.5 ± 7.1	40 (55)	IV	No therapy	L: 7.8 ± 1.25 C: 7.8 ± 1.08	L: 31.2 ± 7.9 C: 31.9 ± 8.0	3.0 g/weeks (3 months)	Hb↑
Higuchi 2016 [19]	Japan	RCT	L: 66 ± 10 C: 67 ± 9	L: 75 (80) C: 73 (80)	Oral	No therapy	L: 11.0 ± 0.9 C: 10.9 ± 0.7	L: 27 ± 7 C: 26 ± 6	140 mg/kg/weeks (12 months)	ERI↓, Hb→
Kletzmayr 1999 [20]	Austria	RCT	L: 54.3 ± 17.0 C: 51.3 ± 15.2	L: 20 (60) C: 20 (45)	IV	Placebo	10 to 12	L: 31.8 ± 12.6 C: 30.8 ± 11.8	5, 25 mg/kg (8 months)	ERI→, ESA doses→
Labonia 1995 [21]	Italy	RCT	L: 41.8 ± 18.6 C: 62.5 ± 7.2	L: 13 (46) C: 11 (45)	IV	Placebo	L_{Hct}: 29.8 ± 2.6 C_{Hct}: 29.1 ± 2.1	L: 41.8 ± 7.1 C: 36.3 ± 9.1	3 g/week (6 months)	ESA doses↓, Hct↑
Maruyama 2017 [11]	Japan	RCT	L: 70 ± 10 C: 69 ± 11	L: 30 (70) C: 30 (57)	IV	No therapy	L: 11.0 ± 1.1 C: 10.8 ± 1.2	–	3 g/week (12 months)	ERI↓, ESA doses↓, Hb→
Mitwalli 2005 [22]	Arabia	RCT	L: 54 ± 15 C: 42 ± 14	L: 18 (39) C: 13 (31)	IV	Placebo	L: 7.89 ± 0.75 C: 7.96 ± 0.35	L: 16.9 ± 6.3 C: 17.5 ± 5.3	45 mg/kg/week (6 months)	Hb↑, Hct↑
Rathod 2006 [23]	India	RCT	L: 40.3 ± 13.6 C: 47.3 ± 11.7	L: 10 (100) C: 10 (80)	IV	Placebo	L: 7.22 ± 0.91 C: 7.28 ± 0.77	–	40 mg/kg/week (8 weeks)	Hb↑
Semeniuk 2000 [28]	Canada	Cross over	66.9 ± 15.9	16 (31)	IV	Placebo	L: 11.3 ± 1.91 C: 11.7 ± 1.31	Carnitine deficiency	60 mg/kg/week (12 weeks)	ESA doses→, Hb→
Singh 2020 [24]	India	RCT	43.2 ± 13.1	40 (58)	IV	No therapy	L: 6.78 ± 1.03 C: 6.66 ± 0.97	–	2 g/week (6 months)	ERI↓, Hb↑
Steiber 2006 [25]	US	RCT	L: 67.6 ± 3.9 C: 69.4 ± 3.4	L: 15 (47) C: 19 (79)	IV	Placebo	L: 11.3 ± 0.4 C: 11.5 ± 0.3	L: 20.6 ± 1.8 C: 19.0 ± 1.4	60 mg/kg/week (24 weeks)	ERI↓, Hb→, Hct→ESA doses↓
Thomas 1999 [26]	Germany	RCT	L: 64.6 ± 14.2 C: 59.5 ± 13.7	L: 9 (33) C: 8 (38)	IV	Placebo	L: 10.4 ± 2.58 C: 10.9 ± 1.75	L: 22.5 ± 5.91 C: 24.3 ± 9.37	30 mg/kg/week (4 months)	Hb→, Hct→
Vaux 2004 [27]	UK	RCT	L: 58.8 ± 19.2 C: 63.8 ± 16.4	L: 13 (77) C: 13 (69)	IV	Placebo	L: 11.5 ± 0.8 C: 12.0 ± 0.9	L: 20.4 ± 6.7 C: 18.9 ± 5.7	60 mg/kg/week (16 weeks)	ESA doses↓, Hb→

L L-carnitine; *C* control; *Hb* hemoglobin; *Hct* hematocrit; *ESA* erythropoiesis-stimulating agent; *ERI* erythropoietin responsiveness index

[a]Intravenous injection after each treatment

[b]Compared with control group, the outcomes showed no difference (→), or decrease (↓) or increase in L-carnitine group (↑)

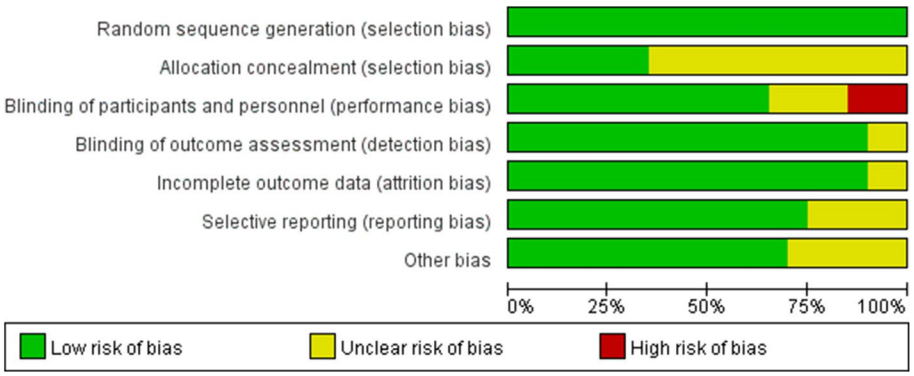

Fig. 2 Risk of bias graph

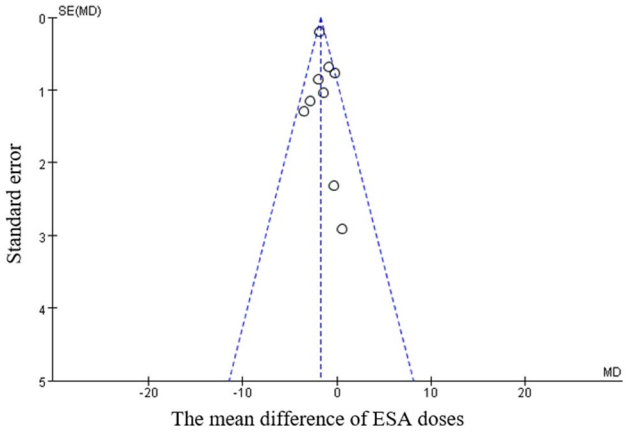

Fig. 3 Funnel plot for ESA doses

Effect of L-carnitine on ESA dose

Nine studies with 456 participants reported the required ESA dose. Compared with the control group, the administration of the required ESA dose significantly decreased in the L-carnitine group throughout the study period (MD: −1.70; 95% CI −2.04 to −1.36; $P < 0.00001$; $I^2 = 15\%$, Fig. 5), with no significant heterogeneity, and the fixed-effect model was used. Subgroup analysis indicated that the effect of L-carnitine on ESA dose reduction was independent of the duration and route (Table 2).

Effects of L-carnitine on hematological parameters

No significant differences were observed in hemoglobin (15 trials with 993 participants; MD: 0.18, 95% CI −0.20 to 0.55, $P = 0.35$, $I^2 = 84\%$, Fig. 6a) and hematocrit (8 trials with 514 participants; MD: 1.07, 95% CI −0.73 to 2.87, $P = 0.24$, $I^2 = 74\%$, Fig. 6b) between the L-carnitine group and the control group, with significant heterogeneity, and the random-effect model were used. To examine the sources of significant heterogeneity of these two pooled effects, the analyses were repeated by removing trials one by one. In each instance, the pooled result and I^2 were quantitatively and qualitatively similar. However, the studies of Cui et al. [16] and Rathod et al. [23] were excluded as the I^2 statistic decreased from 84 to 57% and from 74 to 39%, respectively, suggesting that these two trials might contribute to the heterogeneity. According to the duration and route of L-carnitine treatment, subgroup analysis failed to show significant differences in hemoglobin and hematocrit (Table 2).

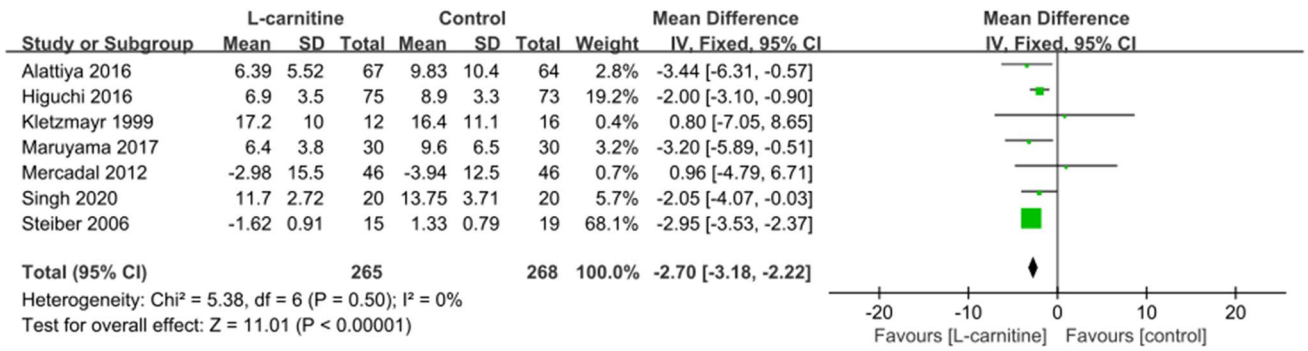

Fig. 4 Forest plot of ERI between L-carnitine group and control group

Table 2 Subgroup analyses of L-carnitine on outcomes according to the duration and route of L-carnitine supplementation

Subgroups	No. of trials	No. of patients		Heterogeneity	MD (95% CI)	*P*-value
		L-carnitine	Control	(I^2, *P*-value)		
ERI						
Route of treatment						
Intravenous	4	77	85	0%, $P=0.66$	−2.88 (−3.42, −2.33)	$P<0.00001$
Oral	2	142	137	0%, $P=0.36$	−2.18 (−3.21, −1.16)	$P<0.0001$
ESA dose						
Duration of treatment						
<6 months	3	53	56	0%, $P=0.48$	−1.20 (−2.38, −0.03)	$P=0.04$
≧6 months	6	171	176	15%, $P=0.32$	−1.73 (−2.08, −1.37)	$P<0.00001$
Route of treatment						
Intravenous	8	200	205	6%, $P=0.38$	−1.67 (−2.01, −1.32)	$P<0.00001$
Oral	1	24	27	–	−3.50 (−6.04, −0.96)	$P=0.007$
Hemoglobin						
Duration of treatment						
<6 months	6	91	93	72%, $P=0.003$	0.49 (−0.19, 1.17)	$P=0.16$
≧6 months	9	438	371	86%, $P<0.00001$	0.02 (−0.40, 0.44)	$P=0.93$
Route of treatment						
Intravenous	12	363	300	87%, $P<0.00001$	0.19 (−0.34, 0.72)	$P=0.49$
Oral	3	166	164	0%, $P=0.80$	0.12 (−0.09, 0.32)	$P=0.26$
Hematocrit (%)						
Duration of treatment						
<6 months	1	8	7	–	−4.00 (−12.67, 4.67)	$P=0.37$
≧6 months	7	282	217	77%, $P<0.0001$	1.25 (−0.58, 3.09)	$P=0.18$

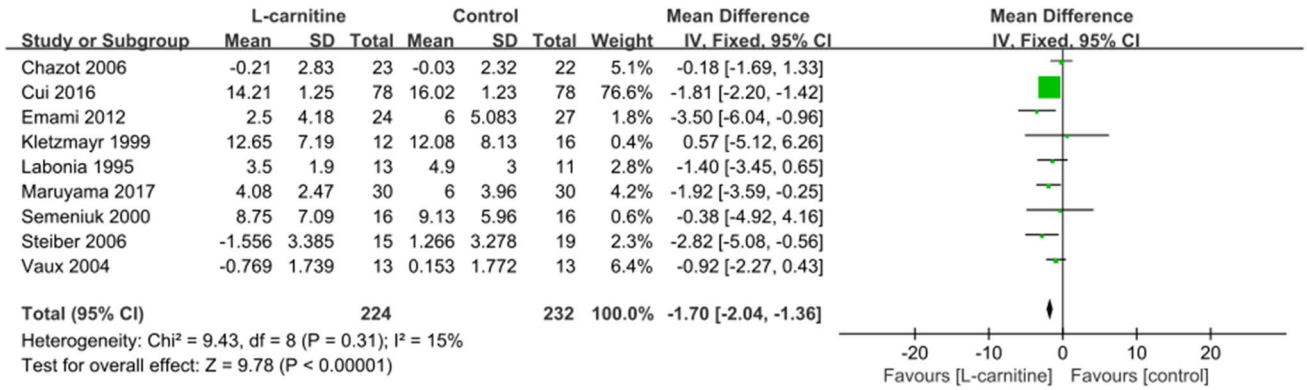

Fig. 5 Forest plot of ESA doses between L-carnitine group and control group

Serum free L-carnitine levels after supplementation

Eleven studies with 715 participants reported the levels of serum free L-carnitine between 2 groups. Compared with the control group, plasma free L-carnitine concentration was increased significantly in the L-carnitine group after L-carnitine supplementation (MD = 140.53 μmol/L, 95% CI 102.22–238.05; $P<0.00001$; $I^2=99\%$, Fig. 7) with significant heterogeneity, and random-effect model was used.

Adverse effects

The trials enrolled in this meta-analysis did not report adverse effects.

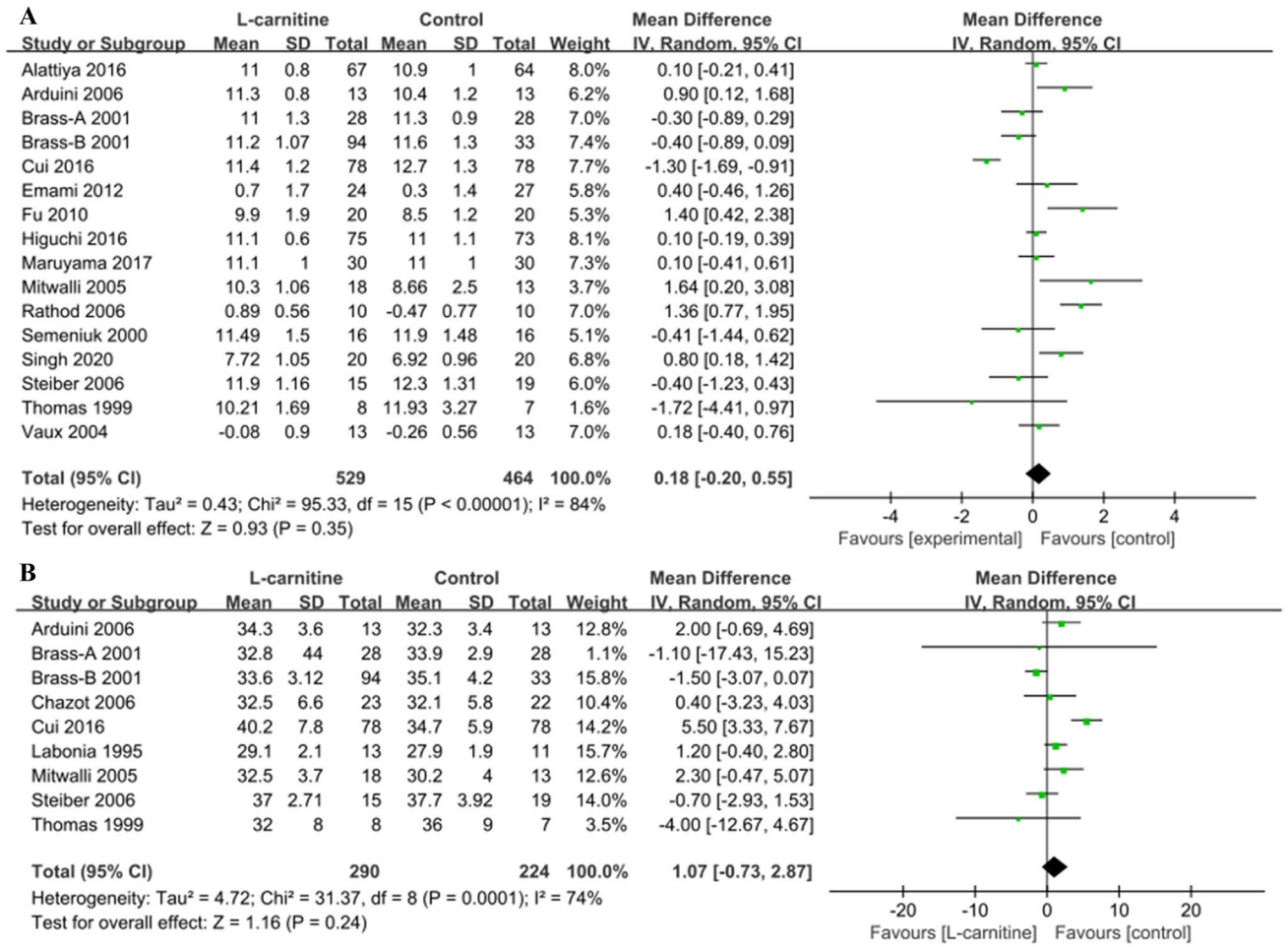

Fig. 6 Forest plot of comparisons in L-carnitine group versus control group. **a** Hemoglobin level; **b** hematocrit level

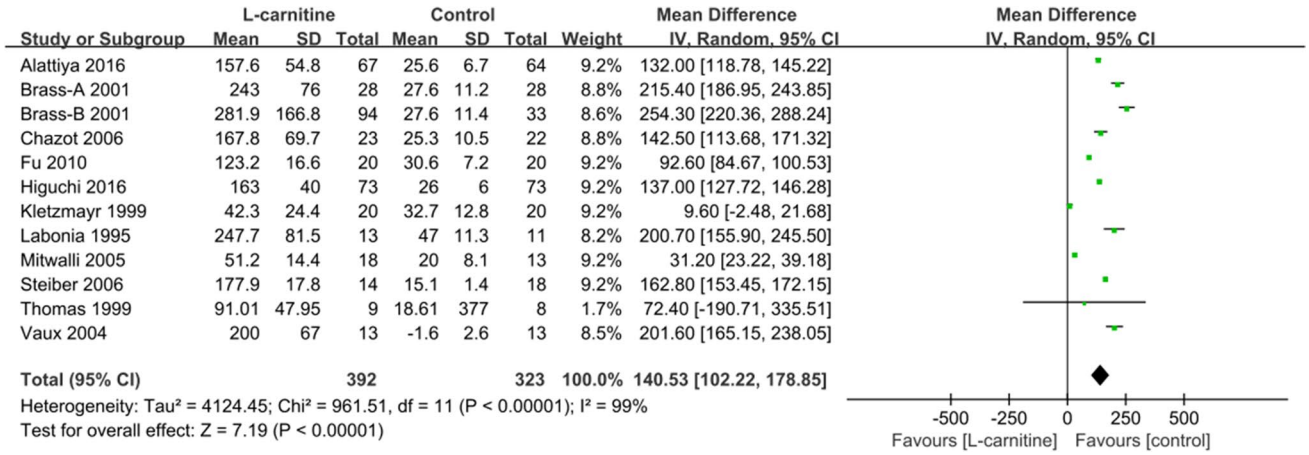

Fig. 7 Forest plot of serum free L-carnitine levels between L-carnitine group and control group

Discussion

Our meta-analysis of 18 RCTs assessed the effect of L-carnitine treatment on renal anemia in patients receiving maintenance hemodialysis. Compared with placebo or no therapy, serum free L-carnitine levels were increased significantly after L-carnitine supplementation. Moreover, L-carnitine treatment was beneficial in decreasing ERI and ESA administration but failed to show differences in hemoglobin and hematocrit levels in patients on hemodialysis. Subgroup and sensitivity analyses produced similar results. L-carnitine treatment seemed to be useful for improving the response to ESA in patients on hemodialysis by maintaining hemoglobin levels and reducing the required ESA doses, independent of the duration and route of L-carnitine treatment.

Most maintenance hemodialysis patients suffer from anemia as a result of iron and EPO deficiency, following fatigue, depression, reduced exercise tolerance, increased mortality related to cardiovascular complications, and an increased risk of hospitalization [29, 30]. The mortality and hospitalization risk of patients can be reduced by 10–12% for every 1 g/dL increase in mean hemoglobin level [30]. The introduction of ESA and intravenous iron is effective in treating renal anemia and avoiding blood transfusions. However, clinical trials have demonstrated that large doses of ESA are associated with higher risks of all-cause mortality and cardiovascular disease independently of hemoglobin, particularly worsening of hypertension. Zhang et al. [31] showed that using higher ESA doses to achieve higher hemoglobin appears to increase the risk of death and cardiovascular outcomes in diabetic hemodialysis patients. A national cohort study that recruited 194,698 hemodialysis patients in Japan also indicated that patients receiving long-term or high-dose ESA had higher mortality than those receiving short-term and low-dose ESAs [32]. In addition, some patients with renal anemia who respond poorly to ESA have difficulty in reaching the target hemoglobin level or hematocrit values even with high-doses of ESA [11]. A decreased hematopoietic response to ESA is linked to inflammation, malnutrition, cardiovascular disease, and a greater risk of death in patients on hemodialysis [13]. In the present meta-analysis, ERI and ESA dose were significantly reduced in the L-carnitine group.

L-carnitine, also called Levocarnitine, is a kind of amino acid that can transport long-chain fatty acids into the mitochondrial matrix to promote lipid metabolism and provide sufficient energy as a form of ATP [9]. 30% of the patents develop L-carnitine deficiency during the period with an onset as early as 3 months after the start of hemodialysis and increase with the duration of dialysis [12]. After a dialysis session, the endogenous plasma L-carnitine level of patients decreases by approximately 60–70%. Moreover, reduced L-carnitine intake, poor intestinal absorption, and impaired L-carnitine synthesis are other causes of L-carnitine depletion in hemodialysis patients. These alterations lead to metabolic disturbances, which might contribute to the development of various clinical complications, such as muscle weakness, cardiac dysfunction, malnutrition, lipid metabolism disorders, anemia, and resistance to EPO in patients undergoing hemodialysis [33]. In this meta-analysis, we found that L-carnitine treatment increased plasma L-carnitine concentrations by 140.53 μmol/L in maintenance hemodialysis patients.

The relationship between L-carnitine and renal anemia has been studied before ESA therapy was available. Labonia et al. [21] and Maruyama et al. [11] demonstrated that intravenous L-carnitine treatment could improve EPO resistance induced by L-carnitine deficiency in dialyzed patients, thereby decreasing the ESA doses. In addition, another RCT revealed that oral L-carnitine supplementation might also increase hemoglobin levels and reduce EPO requirement [17]. Although it was recommended to evaluate the clinical efficacy of L-carnitine every 3 months, a single-blind randomized trial worked by Rathod et al. [23] revealed that intravenous L-carnitine supplementation at a dose of 40 mg/kg/week for 8 weeks improved hemoglobin levels in patients on hemodialysis. The trials included in the current meta-analysis enrolled long-term hemodialysis participants with profound L-carnitine deficiencies (serum free L-carnitine level <40 μmol/L). However, the beneficial effects of L-carnitine on improving the response to ESAs was not observed when the participants were new to hemodialysis (dialysis duration < 6 months) [12]. Although the patients took the generally suggested dose of 1 g after each dialysis and were observed a rapid increase in serum free L-carnitine levels, there was no difference in ESA response between patients with high L-carnitine level and those with physiological level. The main reasons to explain such effects included a low percentage of patients resistant to ESA and half of the placebo patients did not present L-carnitine deficiencies during the study. Additionally, two studies conducted by Brass et al. [14] and Kletzmayr et al. [20] failed to identify the effects of difference doses of L-carnitine on hematological parameters. Our subgroup analysis also showed that the required ESA dose and ERI decreased independent of the treatment duration. The above evidences indicated that L-carnitine offered benefits to patients with profound L-carnitine deficiencies, but may not confirm such an association between beneficial effects and the doses of L-carnitine supplementation.

It should be noted that although no significant difference was observed in hemoglobin and hematocrit levels by L-carnitine therapy in the current meta-analysis, ESA dosing in most included studies changed during the study

when an alteration of hemoglobin of more than 1 g/dL. In addition, the participants with baseline hemoglobin levels higher than 10 g/dL maintained high hemoglobin levels with reduced ESA doses, and increased hemoglobin or/and hematocrit concentrations were observed after L-carnitine supplementation in all trials with the baseline hemoglobin levels below 8 g/dL [16, 18, 22–24]. Nevertheless, the maintenance hemodialysis patients' ultrafiltration and interdialytic weight gain are the culprit issue of erroneous reporting of hemoglobin and hematocrit. The participants in this meta-analysis underwent regular 4-h hemodialysis sessions twice or thrice weekly, and some of the trials reported that the volume of ultrafiltration was determined by clinical dry weight during each session [11, 13–15, 28]. Moreover, the generally recommended method to obtain blood samples was before the start of a hemodialysis session. All of these may reduce the possibility of mistake data in hemoglobin and hematocrit levels.

A previous meta-analysis in 2014 also assessed the effects of L-carnitine treatment on renal anemia in patients receiving hemodialysis [34]. There were some differences between the previous study and our present study. First, the previous study investigated the effect of L-carnitine supplementation on inflammation, oxidative stress, anemia, lipid profiles, myocardial function, coagulation function, and quality of life in hemodialysis patients, whereas the present study focused on renal anemia, including hemoglobin and hematocrit levels, the required ESA doses and ERI value. Second, the study did not support the beneficial effects of L-carnitine on hemoglobin level ($P = 0.35$) and the ESA doses ($P = 0.24$). However, our meta-analysis included some new RCTs, and the results were contrary to the previous finding that L-carnitine decreased the required ESA doses. More importantly, our results indicated that L-carnitine improved the response to ESA in hemodialysis patients.

This meta-analysis had several limitations. First, only 8 out of 18 trials described the concrete randomized methods, and 7 studies did not perform a double-blinding design, which may contribute to the low quality of some trials. Second, all included studies reported short-term duration of L-carnitine treatment (lasting ≦ 1 year), six of which were less than 6 months. As a result, long-term outcomes such as mortality and the risk of cardiovascular disease cannot be evaluated. Third, the heterogeneity reporting hemoglobin and hematocrit was significantly high, and subgroup analyses failed to decrease the heterogeneity. Part of the reasons might be due to the substantial differences in races, L-carnitine dose, and sample size. Fortunately, the heterogeneity in these two results were quantitative, not qualitative.

In conclusion, the present meta-analysis indicated that L-carnitine significantly increased plasma L-carnitine concentrations, improved the response to ESA, decreased the required ESA dose in patients receiving hemodialysis, and maintained hemoglobin and hematocrit levels. L-carnitine supplementation should be supported in hemodialysis patients. However, the relationship between L-carnitine treatment and long-term outcomes is still unclear. Further high-quality RCTs are needed to verify our findings.

Acknowledgements This work was supported by funding from the Natural Science Foundation of Guangxi Province (No.2018GXNSFAA281122), the Development and Application Project of Medical and Health in Guangxi Zhuang Autonomous Region (No. S2017010), NSFC cultivation project of The Second affiliated hospital of Guangxi Medical University (No. GJPY201800), Hengyang Science and Technology Bureau (No. 2014KJ31).

Declaration

Conflict of interest The authors declare that they have no conflicts of interest.

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