Review Article

Effects of Carnitine on Nutritional Parameters in Patients with Chronic Kidney Disease: An Updated Systematic Review and Meta-Analysis

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Abstract

Protein energy malnutrition is a common problem in patients with chronic kidney disease (CKD). Scattered reports indicate that supplementation of Carnitine may improve patients' clinical symptoms, with significant improvement in nutritional parameters. This systematic review was done to document the evidences of Carnitine effects in nutritional status of CKD patients. Peer-reviewed RCTs on Carnitine administration at any dose in CKD patients with at least four weeks of follow-up were including in the meta-analysis. Online databases (PubMed/Medline, ISI Web of Science, Embase, and Scopus) were searched to October 2017 using selected MeSH terms related to the study topic. Data was extracted independently by two reviewers using a standard form and then cross-checked. Statistical analyses were carried out with Comprehensive Meta-analysis software. Data are presented as standard mean difference (SMD) and 95% confidence interval (CI). According to the predefined criteria, a total of 14 randomized controlled clinical trials were included and screened for data extraction by two reviewers, separately. The preliminary results extracted from meta-analysis have shown that Carnitine can significantly increase the levels of albumin (SMD: -0.861; 95% CI: -1.321, -0.402), total protein (SMD: -0.418; 95% CI: -0.695, -0.141), total cholesterol (SMD: -0.350; 95% CI: -0.564, -0.135), LDL cholesterol (SMD: -0.362; 95% CI: -0.551, -0.173), transferrin (SMD: -1.465; 95% CI: -1.822, -1.108), and hemoglobin (SMD: -0.525; 95% CI: -0.732, -0.318); however there were no conclusive effects of Carnitine on body weight (SMD: -0.057; 95% CI: -0.404, 0.291) and BMI (SMD: -0.567; 95% CI: -1.548, 0.415), in pooled analyses. The results of this meta-analysis showed that there are considerable useful pieces of evidence so far about the effect of Carnitine on nutritional factors; however, there is still doubt about some evidences with this regard. It seems necessary to carry out clinical trials with stronger designs to evaluate the impact of these primary outcomes on the patients' clinical conditions. Having this evidences, the potential role of Carnitine in improving malnutrition consequences in CKD patients would be clearly defined.

Keywords: *Carnitine, chronic kidney disease, meta-analysis, nutritional parameters, systematic review*

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Introduction

Chronic kidney disease (CKD) is a global public health problem with an increasing incidence worldwide. It has been estimated that over 2 million people suffered from CKD in the United States in 2014. CKD is defined as the progressive loss of renal function, resulting in irreversible structural damage in nephrons.[1] Despite extensive advancements over the past years in kidney transplantation and dialysis as

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well as novel methods of pharmacotherapy, death is still quite high among dialysis patients compared to a normal population. Malnutrition and inflammation are common issues among patients with CKD. Researches have shown that these two factors may have a substantial role in increasing the risk of death among these patients. Different biochemical factors indicate malnutrition in CKD patients.[2-4] Carnitine deficiency is believed to be one of the factors responsible for various disorders such as anemia, low blood pressure during dialysis, cardiomyopathy, and muscle weakness in dialysis patients. Maintaining the tissue or serum level of carnitine can alleviate some of these disorders.[5,6] Carnitine, as a left-handed isomer (L-carnitine), is a relatively small and hydrophilic molecule, extensively found in milk and meat. Lysine, methionine, ascorbate, niacin, pyridoxine, and iron are among the major sources for the endogenous production of carnitine.[7] As shown in different studies, carnitine has positive clinical effects on patients' inflammatory, nutritional, and lipid factors accompanied with a high risk of cardiovascular diseases, as well as diseases accompanied with carnitine deficiency. Moreover, carnitine can significantly improve patients' physical performance and alleviate exercise intolerance and extreme fatigue, thereby enhancing their quality of life. Other studies have indicated that carnitine may have a role in controlling the serum levels of cholesterol and triglycerides in the normal range while improving anemia and nutritional factors.[8,9]

Nevertheless, reports on the effects of carnitine supplementation in CKD patients are different or, at the time, contradictory. Scattered reports indicate that supplementation of carnitine will improve patients' clinical symptoms, with significant improvement in laboratory parameters, especially on lipid levels and inflammatory and nutritional parameters among hemodialysis patients. On the contrary, there are studies indicating no significant benefit with carnitine supplementation. As a result, assessing the role of carnitine in nutritional status of CKD patients by conducting a systematic review and meta-analysis of the published relevant clinical studies seems rational and promising. Hence, the goal of this paper was to document from randomized controlled trials (RCTs) the effect of carnitine on nutritional parameters in patients with CKD, by systematically reviewing the literature and performing meta-analysis.

Methods

This systematic review and meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline[10,11] and was designed methodologically according to the "standards for systematic reviews."[12-14] The study protocol was submitted in PROSPERO (http://www.crd.york.ac.uk/PROSPERO) with the registered number CRD42015025235.

Data source and search strategy

Online databases (PubMed/Medline, ISI Web of Science, Embase, and Scopus) were searched from January 1970 to October 2017 using selected MeSH terms and free text terms related to the studied topic, including "L-carnitine", "levocarnitine", "carnitine" [using the set operator] AND "nutritional", "albumin", "protein", "weight", "body mass index (BMI)", "BMI","anemia", "hemoglobin", "transferrin", "cholesterol", "low-density lipoprotein (LDL)" [using the set operator] AND "kidney disease", "renal failure", "end-stage renal disease (ESRD)", "CKD", and "dialysis", limited to studies in humans. We also reviewed the references list of the identified publications for additional pertinent studies. No language restrictions were imposed.

Study selection and data extraction

The study selection was done regarding predefined PICOT (Participants/Intervention/Comparison/Outcome/Time) for this review. Peer-reviewed prospective RCTs (parallel group or crossover trials), or retrospective observational studies providing information on the effects of carnitine on nutritional parameters in patients (male/female) of any age with CKD (stages 3, 4, or 5), with at least 4 weeks of follow-up were included in the review the meta-analysis. This was performed by completing the "Defining a question and eligibility criteria" checklist,[15] describing in detail all the elements which would be explored within the review. Carnitine treatment was considered regardless of dosage for more than 4 weeks' administration. For controlled studies, any possible comparator, including placebo or no therapy, was considered. The presence of CKD was defined according to the KDIGO (Kidney Disease: Improving Global Outcomes) guideline.[1]

The primary outcomes were changes in serum albumin (Alb), total protein, weight, BMI, hemoglobin (Hgb), transferrin, cholesterol, and LDL, as compared to control group.

Titles and abstracts were screened independently by two reviewers (clinical pharmacist and nephrologist). Case reports, reviews, editorials, and letters were excluded from qualitative analyses but screened for potential additional references. Data were extracted independently by two reviewers using a standard form designed by the researchers according to the Cochrane Collaboration,[15] and then cross-checked. Any discrepancies were confirmed by a third reviewer.

Quality and risk of bias assessment

Quality of included trials was assessed using CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting RCTs.[16-18] Methodological quality was assessed independently by at least two reviewers according to the Cochrane Collaboration Handbook for systematic reviews.[19,20] Reviewers independently assessed the risk of bias within each included study based on the following domains with ratings of "low risk of bias," "high risk of bias," and "unclear" (uncertain risk of bias); domains included: random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting.

Data analysis

Overall standard mean difference (SMD) and 95% CI (confidence interval) was used to assess the effects of treatment on continuous variables.[20]

Clinical heterogeneity was assessed by comparing the distribution of important participant factors (e.g., administered dose of carnitine, duration of carnitine administration, and …), and trial factors (randomization concealment, blinding of outcome assessment, losses to follow-up, treatment type, and co-interventions). Within and between study heterogeneities were assessed using Cochran's Q-statistics and the heterogeneity test was used to assess the null hypothesis that all studies evaluated the same effect. The effect of heterogeneity is quantified using I^2 which provides a measure of the degree of inconsistency between studies.[21] As we find no evidence of heterogeneity, a fixed effects model was used; otherwise, random effects approach, meta-regression, or subgroup analysis was used in the case of statistical heterogeneity.

Statistical analyses were performed using Comprehensive Meta-analysis (Version 2.2, 2005; Biostat, Englewood, NJ, USA).

Results

The flow diagram of the selection process has been shown in Figure 1. Among the 1065 articles found in different databases, finally, 16 articles underwent quality analysis; while the meta-analysis was performed on 14 articles since the available information was insufficient for analysis in two papers. Main characteristics of these studies are summarized in Table 1.

Study characteristics

Among the 16 included articles for quality analysis, there were 15 articles with randomized controlled clinical design[2,8,22-34] and one article wherein an uncontrolled prospective design had been employed.[35] Finally, 14 articles were included in the quantitative

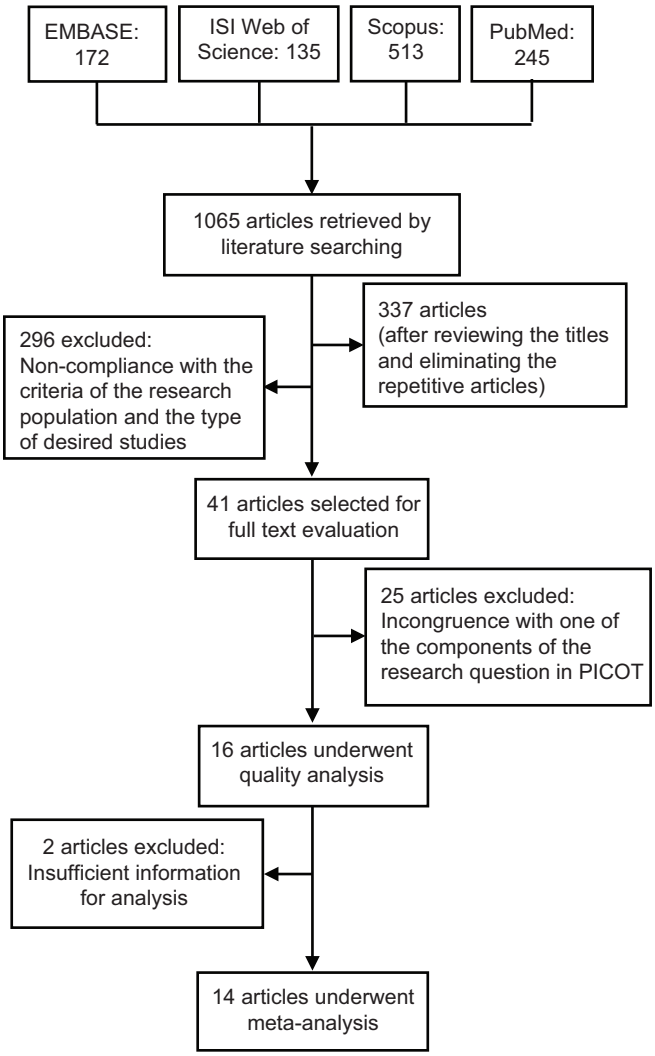

Figure 1: Study selection flow diagram.
PICOT: Participants/Intervention/Comparison/Outcome/Time

analysis, while one of the controlled studies[26] and also one uncontrolled study[35] were excluded after the quality analysis.

A total of 678 individuals constituted the final population of the patients entering into the meta-analysis (from 14 included studies), ranging from 20 to 113 patients participated in each of these studies. In this regard, 315 patients were included in the case group, and 363 patients were included in the control group. All the studies had been carried out on ESRD patients under chronic hemodialysis.

From the total of 14 randomized and controlled clinical trials, in five studies Carnitine was compared with placebo,[8,24,29,31,34] while in nine studies Carnitine was compared with the control group.[2,22,23,25,27,28,30,32,33] In these studies, patients had received Carnitine at a dose of 750–1500 mg per dose. The duration of treatment ranged from 2 to 9 months.

Table 1: Main characteristic of the studies reviewed*

Study, year (reference number)	Study design	Number of patients	Intervention	Duration (months)	Outcomes
Excluded studies					
Kudoh *et al*., 2014[35]	Prospective uncontrolled study	20 (male: 10, female: 10)	L-carnitine 900 mg/dose	12	Alb, Hgb, total cholesterol, LDL
Khodaverdi *et al*., 2009[26]	Randomized triple-blind clinical trial	29 (carnitine: 14; control: 15)	L-carnitine 1000 mg/dose	3	Hgb
Included studies					
Veselá *et al*., 2001[22]	Randomized controlled clinical trial	21 (carnitine: 9; control: 12); male: 25, female: 20	L-carnitine 1000 mg/dose	6	Alb, total protein, total cholesterol, LDL
Chazot *et al*., 2003[23]	Randomized controlled clinical trial	45 (carnitine: 23; control: 22)	L-carnitine 1000 mg/dose	6	Alb, body weight, BMI, total cholesterol
Savica *et al*., 2005[34]	Pilot study, placebo-controlled	113 (carnitine: 48; control: 65); male: 63, female: 50	L-carnitine 1500 mg/dose	6	Alb, BMI, Hgb, transferrin
Rathod *et al*., 2006[24]	Randomized, Single-blind, placebo-controlled clinical trial	20 (carnitine: 10; control: 10); male: 18, female: 2	L-carnitine 1500 mg/dose	2	Alb, Hgb, total cholesterol, LDL
Duranay *et al*., 2006[25]	Randomized controlled clinical trial	42 (carnitine: 21; control: 21); male: 24, female: 18	L-carnitine 1500 mg/dose	6	Alb, total protein, body weight, BMI, transferrin, total cholesterol, LDL
Sabry *et al*., 2010[27]	Randomized controlled clinical trial	55 (carnitine: 20; control: 35); male: 35, female: 19	L-carnitine 1500 mg/dose	6	Hgb
Fu *et al*., 2010[28]	Randomized, double-blind, controlled trial	40 (carnitine: 20; control: 20); male: 22, female: 18	L-carnitine 1000 mg/dose	3	Pre-Alb, Alb, LDL, total protein, total cholesterol, Hgb
Mortazavi *et al*., 2011[29]	Randomized, placebo-controlled, single-blind trial	48 (carnitine: 24; control: 24)	L-carnitine 750 mg/dose	9	Alb, Hgb, total cholesterol, LDL
Suchitra *et al*., 2011[2]	Randomized, single-blind trial	35 (carnitine: 20; control: 15); male: 22, female: 13	L-carnitine 1000 mg/dose	6	Alb, total protein, total cholesterol, LDL
Emami Naini *et al*., 2012[30]	Controlled clinical trial	60 (carnitine: 30; control: 30); male: 38, female: 22	L-carnitine 750 mg/dose	2	Total cholesterol, LDL
Mortazavi *et al*., 2012[8]	Randomized, placebo-controlled, double-blind clinical trial	36 (carnitine: 17; control: 19)	L-carnitine 750 mg/dose	6	Alb, Hgb, total cholesterol, LDL
Emami Naini *et al*., 2012[31]	Randomized, placebo-controlled, double-blind trial	51 (carnitine: 24; control: 27); male: 26, female: 25	L-carnitine 900 mg/dose	4	BMI, Hgb, LDL
Fukami *et al*., 2013[32]	Randomized, comparator-controlled trial	70 (carnitine: 32; control: 38); male: 44, female: 26	L-carnitine 900 mg/dose	6	Alb, Hgb, total protein, LDL
Ahmadi *et al*., 2016[33]	Randomized clinical trial	42 (carnitine: 17; control: 25)	L-carnitine 1000 mg/dose	3	Body weight, BMI

*For all included studies, study population consisted ESRD patients on chronic hemodialysis. ESRD=End stage renal disease, Alb=Albumin, Hgb=Hemoglobin, LDL=Low-density lipoprotein (cholesterol), BMI=Body mass index

Study quality and risk of bias

The risk of the incidence of possible errors in RCTs is summarized in Table 2. The details of randomization method had been described in seven studies,[8,24,25,29-31,33] and the details of the blinding method for the assignment of each patient to the case and control groups (allocation concealment) had been described in four studies.[2,8,24,31] Hence, these studies had a low risk for the occurrence of these errors. Four studies had double-blinded design.[8,28,30,31] However, other studies had not provided any information on the above-mentioned items and thereby, had a high risk of occurrence of

Table 2: Risk of the incidence of possible errors in studies reviewed*

Study, year (reference number)	Random sequence generation	Blinding of participants and outcome assessors	Incomplete outcome data
Veselá *et al*., 2001[22]	Unclear (not stated)	Unclear (not stated)	High risk (overall dropout 12.5%; 25% vs. 0% in carnitine vs. control groups)
Chazot *et al*., 2003[23]	Unclear (not stated)	Unclear (not stated)	High risk (overall dropout 15%; 17.8% vs. 12% in carnitine vs. control groups)
Savica *et al*., 2005[34]	Unclear (not stated)	Unclear (not stated)	Unclear (not reported)
Rathod *et al*., 2006[24]	Low risk ("randomization through a table generated by a computer program")	Low risk (patient blind)	High risk (overall dropout 23%)
Duranay *et al*., 2006[25]	Low risk ("randomization through systemic random sampling method")	Unclear (not stated)	Low risk (no dropout)
Sabry *et al*., 2010[27]	Unclear (not stated)	Unclear (not stated)	Unclear (not reported)
Fu *et al*., 2010[28]	Unclear (not stated)	Unclear (not stated)	Low risk (no dropout)
Mortazavi *et al*., 2011[29]	Low risk ("randomization through a table generated by a computer program")	Low risk (double blind)	High risk (overall dropout 12.7%; 14.3% vs. 11.11% in carnitine vs. control groups)
Suchitra *et al*., 2011[2]	Unclear (not stated)	Unclear (not stated)	Low risk (no dropout)
Emami Naini *et al*., 2012[30]	Low risk ("randomization through statistical randomization methods")	Low risk (double blind)	Unclear (not reported)
Mortazavi *et al*., 2012[8]	Low risk ("randomization through statistical randomization methods")	Low risk (double blind)	High risk (overall dropout 27.7%)
Emami Naini *et al*., 2012[31]	Low risk ("randomization through random allocation software")	Low risk (double blind)	Low risk (overall dropout rate 5%)
Fukami *et al*., 2013[32]	Unclear (not stated)	Unclear (not stated)	High risk (overall dropout 31.3%; 37.2% vs. 25.5% in carnitine vs. control groups)
Ahmadi *et al*., 2016[33]	Low risk ("randomization through random allocation software")	Unclear (not stated)	High risk (overall dropout 16%; 32% vs. 0% in carnitine vs. control groups)

*For all included studies, allocation concealment and selective reporting was 'Unclear (not stated)'. Also, other sources of bias were 'Unknown'

these errors. Reporting bias (the possibility of selective reporting of the results) was unknown in all studies.

Outcome data

The outcome information was extracted and analyzed as follows: Alb in nine papers, weight and BMI in three articles, serum concentrations of Hgb and transferrin, respectively, in seven and two articles, the amount of total protein in five articles, total cholesterol in nine articles, and LDL in nine articles. This information is shown in Table 3.

Effects of Carnitine on primary and secondary outcomes

The results of meta-analysis conducted on outcome parameters are shown in Table 3 and Figures 2-9.

Albumin

Results of meta-analysis of the effects of Carnitine on Alb concentration are shown in Table 3 and Figure 2. Due to the I^2 acquisition of 76.6%, the results of this test on the variable of Alb indicate that there is much heterogeneity between the studies. Therefore, random effects meta-analysis was used to reduce the impact of this heterogeneity. In addition, meta-regression was also conducted to investigate the effect of potential confounding factors as a source of heterogeneity.

In terms of the duration of carnitine administration, the prescriptions above 4 months were considered among the effective factors in the response rate to this medicine; the meta-regression results were significant only for the studies with a duration of more than 4 months ($P < 0.001$) and were not significant for the studies with lower than 4 months in length ($P = 0.407$).

Furthermore, in terms of carnitine dose, the meta-regression results were significant only for the studies at a dose of 1500 mg ($P < 0.001$) and were not significant for studies at a dose of 1000 ($P = 0.062$) or <1000 mg ($P = 0.091$).

Total cholesterol

The results of heterogeneity test on the variable of total cholesterol were indicative of a moderate non-significant heterogeneity among the studies ($P = 0.168$;

Table 3: Results of meta-analysis conducted on outcome parameters

Primary outcome	Articles included in meta-analysis (reference number)	Total number of patients	SMD	95% CI	Test for overall effect	Effect of carnitine administration (in the case group compared to the control group)	I^2 test of heterogeneity	Meta-analysis
Alb	9 controlled studies[2,8,22-25,28,32,34]	402	−0.861	−1.321, −0.402	Z=−3.672 (P<0.001)	Significant effect (increasing trend) on the concentration of Alb	I^2: 76.6% high heterogeneity among the studies (P<0.001)	Random effects analysis
Total protein	5 randomized controlled clinical trials[2,22,25,28,32]	208	−0.418	−0.695, −0.141	Z=−2.954 (P=0.003)	Significant effect (increasing trend) on the concentration of total protein	I^2: 2.51% low heterogeneity among the studies (P: 0.392)	Fixed effects analysis
Body weight	3 randomized controlled clinical trials[23,25,33]	129	−0.057	−0.404, −0.291	Z=−0.319 (P=0.750)	Nonsignificant effect on the patient's weight	I^2: 0.001% low heterogeneity among the studies (P: 0.983)	Fixed effects analysis
BMI	3 randomized controlled clinical trials[25,33,34]	197	−0.567	−1.548, −0.415	Z=−1.131 (P=0.750)	Nonsignificant effect on the patient's BMI	I^2: 86.2% high heterogeneity among the studies (P<0.001)	Random effects analysis
Total cholesterol	9 randomized controlled clinical trials[2,8,22-25,28-30]	347	−0.350	−0.564, −0.135	Z=−3.199 (P=0.001)	Significant changes (increasing trend) in total cholesterol levels	I^2: 31.3% moderate nonsignificant heterogeneity among the studies (P: 0.168)	Fixed effects analysis
LDL cholesterol	9 randomized controlled clinical trials[2,8,22,24,25,28-30,32]	442	−0.362	−0.551, −0.173	Z=−3.750 (P<0.001)	Significant changes in LDL levels	I^2: <0.01% low heterogeneity among the studies (P: 0.608)	Fixed effects analysis
Transferrin	2 controlled studies[25,34]	155	−1.465	−1.822, −1.108	Z=−8.042 (P<0.001)	Significant effect (increasing trend) on the concentration of transferrin	I^2: <0.01% low heterogeneity among the studies (P: 0.628)	Fixed effects analysis
Hgb	7 controlled studies[8,24,27-29,32,34]	382	−0.525	−0.732, −0.318	Z=−4.969 (P<0.001)	Significant changes in total Hgb levels	I^2: 35.6% moderate nonsignificant heterogeneity among the studies (P: 0.156)	Fixed effects analysis

SMD=Standard mean difference, CI=Confidence interval, BMI=Body mass index, LDL=Low-density lipoprotein, Alb=Albumin, Hgb=Hemoglobin

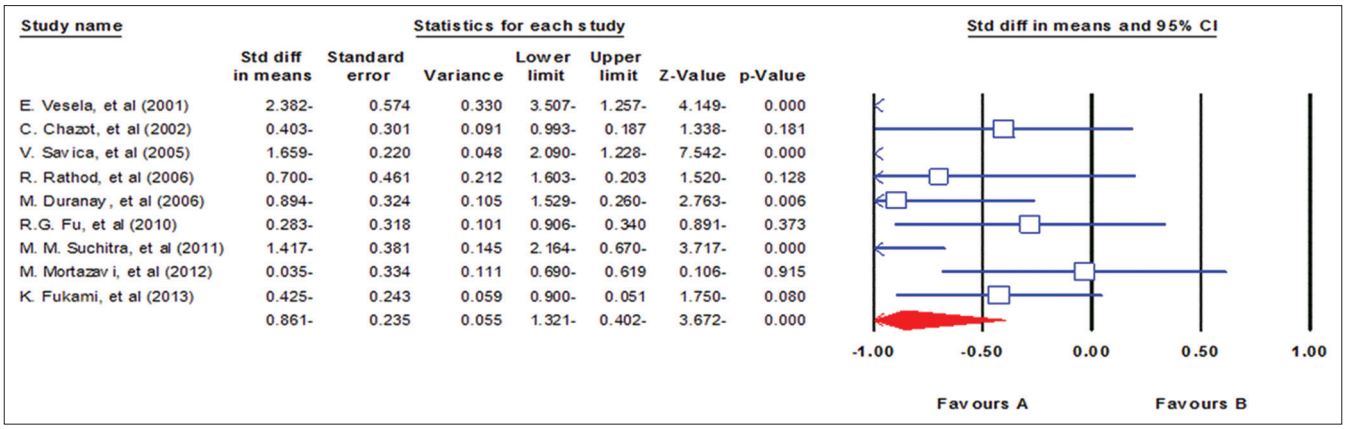

Figure 2: Forest plot of meta-analysis on albumin (9 studies)

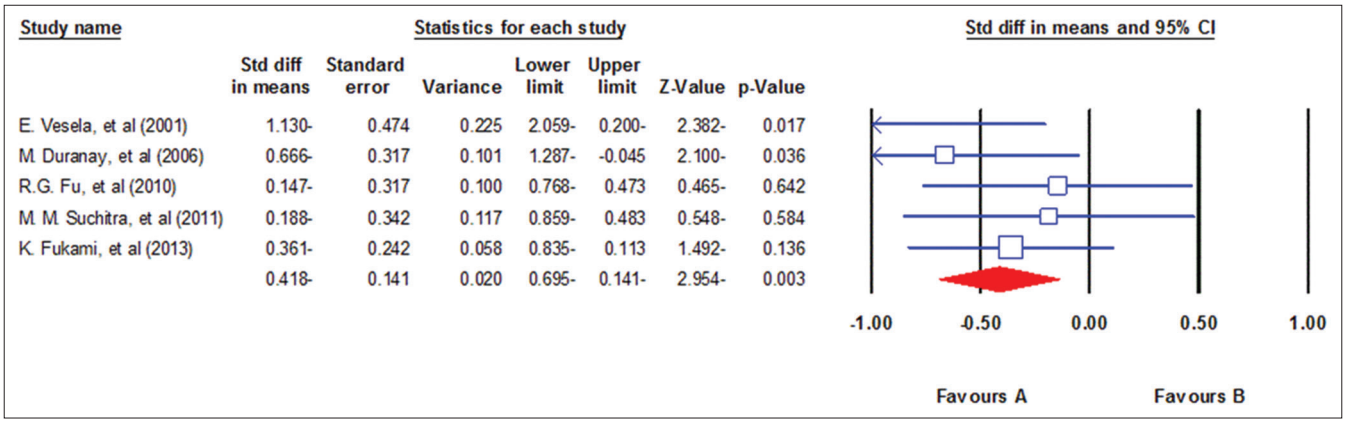

Figure 3: Forest plot of meta-analysis on total protein (5 studies)

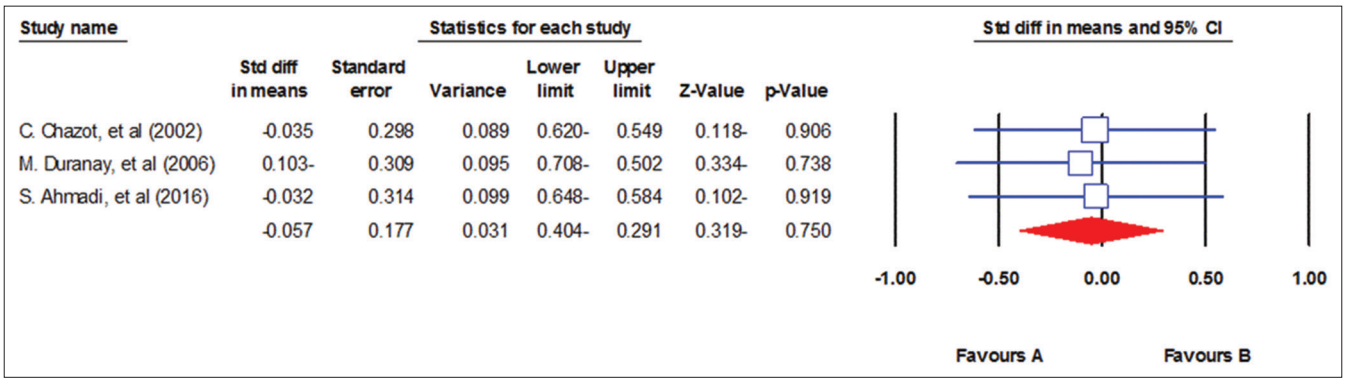

Figure 4: Forest plot of meta-analysis on body weight (3 studies)

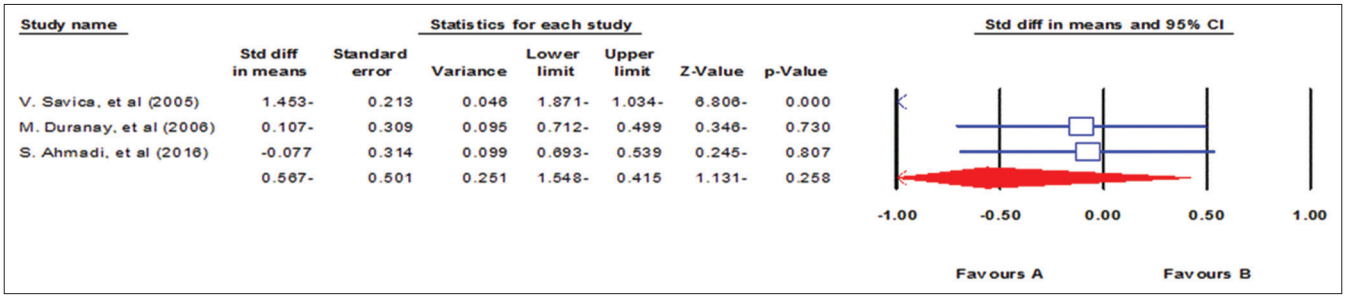

Figure 5: Forest plot of meta-analysis on body mass index (3 studies)

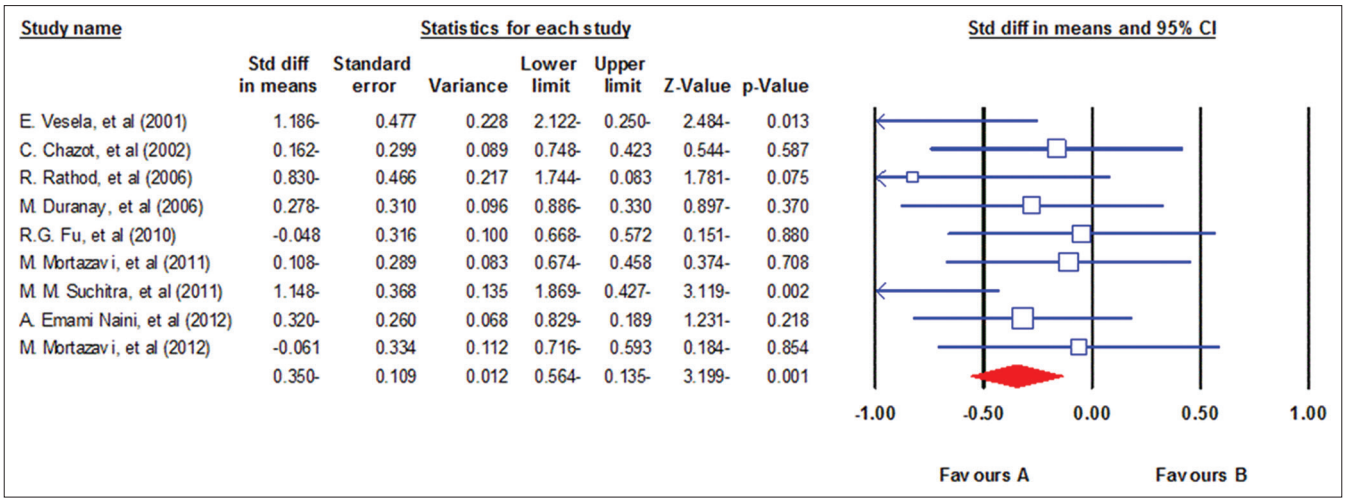

Figure 6: Forest plot of meta-analysis on total cholesterol (9 studies)

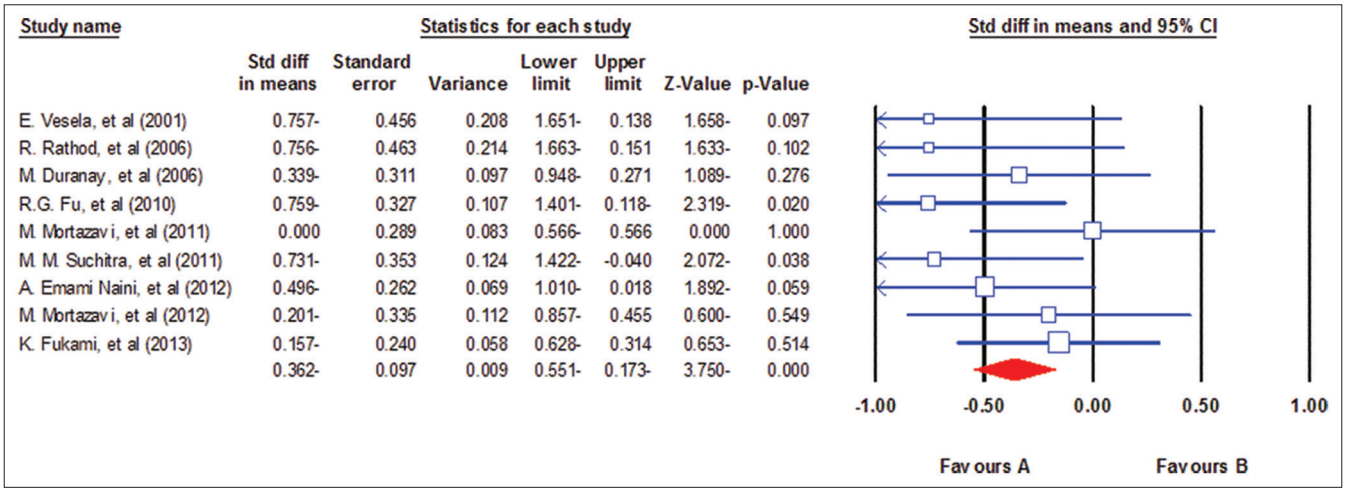

Figure 7: Forest plot of meta-analysis on low-density lipoprotein cholesterol (9 studies)

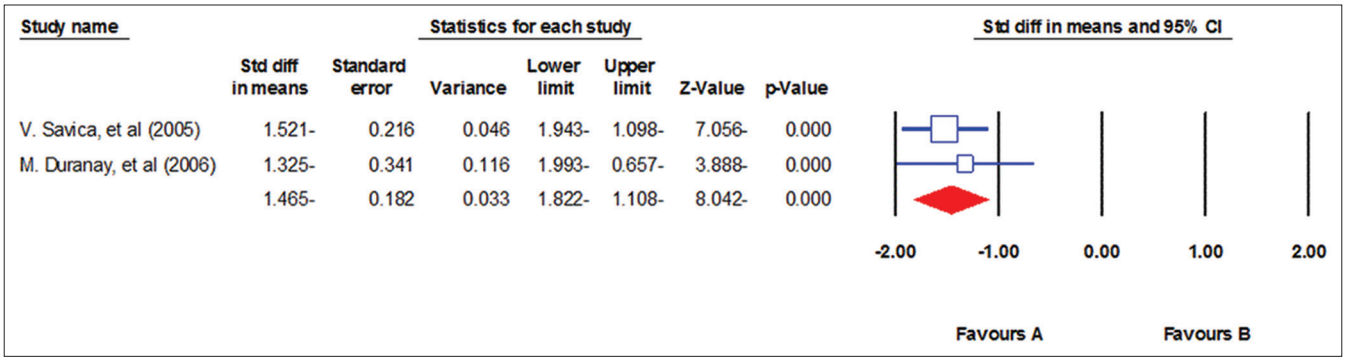

Figure 8: Forest plot of meta-analysis on transferrin (2 studies)

I^2 =31.3%). However, meta-regression was also carried out to investigate the effect of potential confounding factors on the rate of the changes in total cholesterol concentrations in response to carnitine prescription. In this regard, the L-carnitine dose, and the duration of medicine administration were considered as the confounding factors.

In terms of the duration of medicine administration, the prescriptions above 4 months were among the effective factors in the response rate to medicine ($P < 0.001$). However, in terms of medicine dose, the meta-regression results were not statistically significant for the studies with different doses.

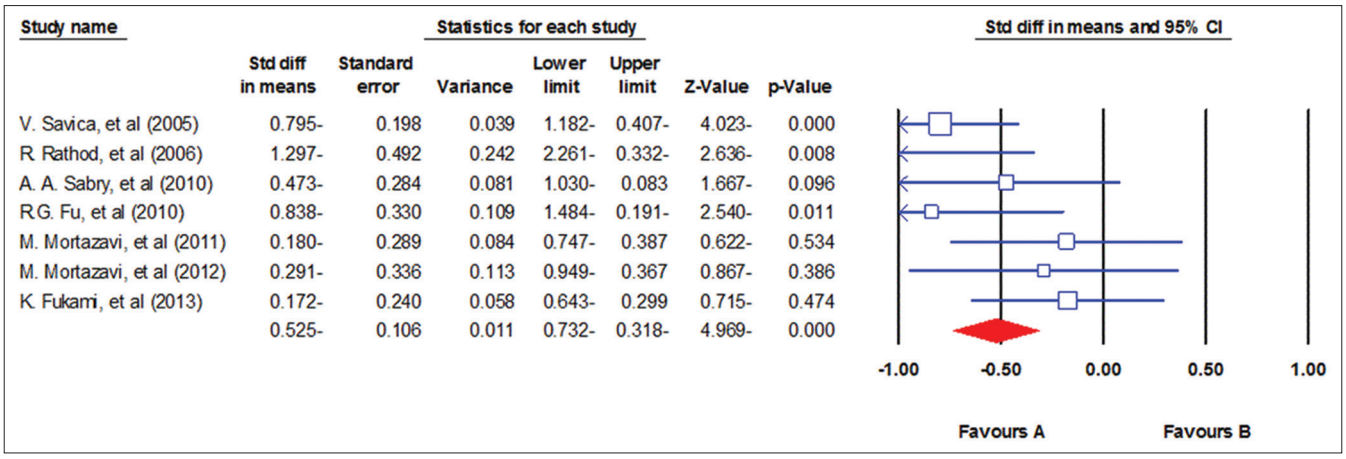

Figure 9: Forest plot of meta-analysis on hemoglobin (7 studies)

Hemoglobin

The results of heterogeneity test on the studies evaluating the Hgb level were indicative of a moderate non-significant heterogeneity among the studies ($P = 0.156$; $I^2 = 35.6\%$). However, meta-regression was also carried out to investigate the effect of potential confounding factors on the rate of the changes in Hgb level concentrations in response to carnitine prescription. However, with regard to the mentioned confounding factors, the meta-regression results were not significantly different for studies with different doses and durations of Carnitine administration.

Subgroup analysis

Since a small number of articles for each variable were analyzable in this review, it was not possible to conduct a valid subgroup analysis in terms of the type and design of studies, the demographic characteristics of the populations, the rate of kidney failure at the start of the study, baseline levels of the variables, and other simultaneous treatments that had been included in the study protocol from the beginning.

Only some variables underwent subgroup analysis and meta-regression regarding the dose and duration of carnitine administration as confounding factors; so the role of these factors as a source of heterogeneity was examined among the studies. The results of the analysis have been presented for each variable.

Discussion

This review aimed to collect and analyze the pieces of evidence about the possible positive effects of carnitine administration in improving nutritional factors in CKD patients. Carnitine is an essential factor for the membrane transfer of Acyl-CoA compounds, especially for the transmission of long-chain fatty acids to the mitochondria. Carnitine has a very important role in the beta-oxidation of fatty acids which promotes the breakdown of fatty acids for the synthesis of triglycerides.[22,23]

In numerous clinical studies, it has been shown that the administration of carnitine in patients with kidney failure has improved various disorders, such as heart problems, intolerance, and capacity reduction in activity, muscle cramps, low blood pressure during dialysis, and anemia resistant to erythropoietin.[36-38]

According to the results obtained from the systematic searches of resources, evidence in this area were limited to a uncontrolled and low-quality study,[35] as well as randomized controlled studies (comparing the effect of carnitine with placebo or standard treatment) with acceptable quality, but small sample size.[22,24] Some of these studies had not been primarily aimed to determine the clinical effect of carnitine on nutritional factors and had provided some information solely in terms of the biomarkers and index factors related to the expected outcomes in this study. Therefore, the low sample size of these studies probably does not provide sufficient power to make a meaningful conclusion about the therapeutic effects of carnitine on specified biomarkers.

In this meta-analysis, it is revealed that carnitine may have the beneficial role to improve the pattern of all studied nutritional parameters including levels of serum Alb, total protein, total cholesterol, LDL cholesterol, transferrin, and Hgb, while it has not any significant effect on body weight or BMI of the studied CKD patients.

It is important to note that all the reviewed studies had provided some information on the effect of carnitine on nutritional factors, while these parameters are, in fact, the substitute outcomes not the main malnutrition consequences. Poor control of malnutrition in CKD patients is associated with the

incidence of worse consequences in the cardiovascular system and poor quality of life, especially in dialysis patients.[36] Therefore, the studies that explore new treatments should clarify this point whether or not the possible improvements in nutritional factors actually lead to real clinical benefits in the long run. Among the studies that were analyzed, only two studies[24,31] had presented some information about the effect of treatment with carnitine on quality of life. In this regard, Rathod *et al*.[24] had shown the positive effects of Carnitine on quality of life, but Emami Naini *et al*. study[31] did not report any significant differences between Carnitine and placebo groups, considering patients' quality of life. Therefore, there is contradictory evidence in this regard, and further studies are needed to be conducted. On the other hand, the target population of patients who benefits most from the administration of carnitine is still not known. The improvement of nutritional factors in CKD patients under chronic dialysis is much more difficult than the early stages of CKD due to other comorbidities and higher rates of inflammation in this population.[5,6]

Strengths and weaknesses of the study

Before conducting this review study, its protocol had been criticized and registered in the International Database "PROSPERO." Search of articles for including in the study was done in a systematic manner and through a comprehensive review of different databases related to the field of medicine to reduce the possibility of publication bias. In addition, a systematic and structured method was employed to extract and analyze the data in accordance with the current standards for systematic review studies. It was attempted to use two researchers (a clinical pharmacist and a nephrologist) whenever possible to go through most of the stages, including the comprehensive search of resources, information extraction, and especially the quality assessment of articles. Another noteworthy strength of this study was the fact that no restrictions were imposed in terms of the publication language of the articles, so two articles in the Persian language are also included in the study during the initial search.

The main limitation of this study was the exclusive search of electronic internet resources. Furthermore, most of the selected studies had a small sample size, and limited number of studies had provided information about the similar consequences. This limited the reliability of the findings of this meta-analysis and made us unable to do a comprehensive analysis on the subgroups for specifying the moderating factors influencing the effects of this drug. In addition, the existing heterogeneities in the patients' population entering the studies, particularly with regard to the L-carnitine dose and the duration of intervention, as well as other patients' concurrent medications, made it impossible to draw definitive conclusions for some variables. Thus, these findings cannot be generalized to the entire population of CKD patients.

Conclusion

The results of this meta-analysis showed that there are considerable useful pieces of evidence so far about the effect of carnitine on nutritional factors; however, considering the shortages previously described, there is still doubt about some evidence with this regard. Furthermore, it is noticeable that this conclusion has been extracted from some small and heterogeneous studies based on related biomarkers. Therefore, it is necessary to carry out clinical trials with stronger designs to evaluate the impact of these primary outcomes on the patients' clinical conditions. Having this evidence, the potential role of carnitine in improving malnutrition consequences in CKD patients would be clearly defined.

Authors' Contribution

Tahereh Gholipur-Shahraki contributed in searching databases and extracted data from selected articles. Awat Feizi performed meta-analysis. Mojgan Mortazavi contributed in study concept and quality analysis of selected articles. Shirinsadat Badri contributed in searching databases, data extraction and quality analysis of selected articles. All authors contributed in manuscript preparation and final editing.

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Conflicts of interest

There are no conflicts of interest.

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