European Journal of Clinical Pharmacology (2019) 75:1037–1046
https://doi.org/10.1007/s00228-019-02666-5

REVIEW

The effect of L-carnitine on inflammatory mediators: a systematic review and meta-analysis of randomized clinical trials

F. Haghighatdoost[1,2] · M. Jabbari[3] · Mitra Hariri[4]

Received: 13 January 2019 / Accepted: 7 March 2019 / Published online: 26 March 2019

Abstract

Aim and background Reducing inflammation by nutritional supplements may help to reduce the risk of many chronic diseases. Our aim in this meta-analysis was to determine the effect of L-carnitine on inflammatory mediators including C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6).

Methods Our systematic search to find relevant randomized clinical trials (RCTs) was performed up to October 2018 using ISI Web of Science, Google Scholar, PubMed/Medline, and SCOPUS. In this meta-analysis, the weighted mean differences (WMD) with standard errors (SE) were used to pool the data. WMD was calculated by subtracting change-from-baseline mean values in the control group from change-from-baseline mean values in the intervention group in each study. To identify heterogeneity among studies, the I^2 statistic was employed. The protocol was registered with PROSPERO (No. CRD42019116695).

Results Thirteen articles were included in our systematic review and meta-analysis. The results of the meta-analysis indicated that L-carnitine supplementation was significantly associated with lower levels of CRP in comparison to controls (WMD = −1.23 mg/L; 95% CI: −1.73, −0.72 mg/dL; $P < 0.0001$). Also, a slight but statistically significant decrease was observed in IL-6 and TNF-α levels (WMD = −0.85 pg/dL; 95% CI: −1.38, −0.32 pg/dL; $P = 0.002$ and WMD = −0.37 pg/dL; 95% CI: −0.68, −0.06 pg/dL; $P = 0.018$, respectively).

Conclusion Our results indicate that L-carnitine reduced inflammatory mediators, especially in studies with a duration of more than 12 weeks. Further studies with different doses and intervention durations and separately in men and women are necessary.

Keywords L-carnitine · Interleukin-6 · Tumor necrosis factor-alpha · C-reactive protein

Introduction

Over the past decade, the relationship between atherosclerosis and inflammation has been widely studied (Table 1). A large body of evidence suggests that the process of atherosclerotic disease is correlated with inflammatory mediator levels. Higher inflammation status can cause development of coronary artery disease (CAD) [1, 2]. In human studies, the levels of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) have been used to predict the risk for CAD [3–5]. Reducing inflammation through nutritional supplements may be able to lower the risk of many chronic diseases [6–8].

L-carnitine (β-hydroxy-γ-trimethyl-amino-butyric acid, LC) is an essential compound which is synthesized in the kidneys and liver from lysine and methionine or supplied to body by dietary sources such as meat and dairy products [9]. LC is also a necessary cofactor for fatty acid β-oxidation and facilitates long-chain fatty acid transportation across the inner membrane of mitochondria. Therefore, lack of LC impairs the use of fatty acids as fuel [10, 11].

LC is also used as a dietary supplement and has gained popularity with recent reporting of suggested anti-inflammatory properties [12–15]. LC might be able to reduce inflammation by modulating the function of inflammatory

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00228-019-02666-5) contains supplementary material, which is available to authorized users.

✉ Mitra Hariri
Haririm1@nums.ac.ir

[1] Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

[2] Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran

[3] Department of Public Health, School of Paramedical and Health, Zanjan University of Medical Sciences, Zanjan, Iran

[4] Department of Basic Medical Sciences, Neyshabur University of Medical Sciences, Neyshabur, Iran

Table 1 Randomized controlled trials included in the systematic review and meta-analysis

Code Author (year) (country)	Subjects and gender	Age (years) and BMI (kg/m^2) (mean ± SD)	Randomized clinical trial	Intervention	Placebo	Duration (weeks)	Variables	Results	Score
1 Badrasawi, M. 2016 Malaysia 20	Pre-frail older subjects M = 23 F = 27 *N* = 50	Age: 68.2 ± 6.3 BMI: 20.1 ± 1.4	Randomized, double-blind, placebo-controlled study	L-carnitine 1.5 g/day	Not mentioned	10	CRP, IL-6	No significant change in CRP and IL-6	5
2 Bloomer, R. J. 2009 USA 21	Pre-diabetic patients *N* = 29 F = N/M M = N/M	Age: 31 ± 10.8 BMI: 28.5 ± 1.9	Randomized, double-blind, placebo-controlled study	L-carnitine 4 g/day	Cellulose	8	CRP	No significant change in CRP	7
3 Dastan, F. 2018 Iran 22	Patients who underwent coronary artery bypass graft surgery (CABG) *N* = 134 M = 99 F = 35	Age: 60.0 ± 9.2 BMI: 28.2 ± 4.5	Randomized controlled trial	L-carnitine 3000 mg/day + coronary artery bypass graft surgery	Coronary artery bypass graft surgery	5 days	CRP	CRP reduced significantly	5
4 Derosa, G. Italy 2010 23	Type 2 diabetes mellitus *N* = 258 M = 127 F = 131	Age: 53 ± 6 BMI: 33.1 ± 2.9	Randomized, double-blind, controlled study	Orlistat 120 mg three times a day plus L-carnitine 2 g once daily	Orlistat 120 mg three times a day	48	CRP	CRP reduced significantly	6
5 Derosa, G Italy 2011 13	Type 2 diabetes patients *N* = 258 M = 127 F = 131	Age: 53 ± 6 BMI: 33.1 ± 2.9	Randomized, double-blind, controlled study	Orlistat 120 mg three times a day plus L-carnitine 2 g once daily	Orlistat 120 mg three times a day	48	TNF-α	TNF-α reduced significantly	8
6 Derosa, G Italy 2010 24	Uncontrolled type 2 diabetes mellitus *N* = 123 M = 113 F = 110	Age: 54 ± 5 BMI: 33.4 ± 3.2	Randomized, double-blind, controlled study	Sibutramine 10 mg plus L-carnitine 2 g	Sibutramine 10 mg	48	CRP, TNF-α	CRP and TNF-α reduced significantly	6
7 Hakeshzadeh, F. 2010 Iran 25	Hemodialysis patients *N* = 36 M = 15 F = 21	Age: 48 ± 10 BMI: 24 ± 4	Randomized, double-blind, placebo-controlled trial	1000 mg/day oral L-carnitine	Not mentioned	12	CRP	CRP reduced significantly	5
8 Jirillo, E 1991 Italy 26	Active pulmonary tuberculosis *N* = 20 F = 10 M = 10	Age: 49 ± 17 BMI: N/M	Randomized, double-blind, placebo-controlled trial	L-carnitine 2 g/day	Not mentioned	4	TNF-α	No significant change in TNF-α	8

Table 1 (continued)

Code Author (year) (country)	Subjects and gender	Age (years) and BMI (kg/m^2) (mean ± SD)	Randomized clinical trial	Intervention	Placebo	Duration (weeks)	Variables	Results	Score
9 Lee, B. J. 2015 Taiwan 14	Coronary artery disease patients N = 39 M = 39	Age: 72.7 ± 10.1 BMI: 26 ± 2.4	Randomized, single-blind, placebo-controlled trial	L-carnitine 1000 mg/day	Starch	12	IL-6, TNF-α, CRP	IL-6, TNF-α, and CRP reduced significantly	5
10 Malaguarnera, M. 2010 Italy 27	Nonalcoholic steatohepatitis *N* = 74 M = 40 F = 34	Age: 47.8 ± 5.8 BMI: 26.5 ± 3.8	Randomized, double-blind, placebo-controlled study	L-carnitine 2000 mg/day	Not mentioned	24	TNF-α, CRP	TNF-α and CRP reduced significantly	4
11 Malek Mahdavi, A. 2016 Iran 12	Women with knee osteoarthritis *N* = 69 F = 69	Age: 51.63 ± 5.69 BMI: N/M	Randomized, double-blind, placebo-controlled study	750 mg/day L-carnitine	Not mentioned	8	CRP	No significant change in CRP	7
12.1 Rafraf, M. 2015 Iran 28	Healthy obese women *N* = 22 F = 22	Age: 34.40 ± 5.48 BMI: 33.99 ± 2.33	Randomized, double-blind, placebo-controlled study	2 g/day L-carnitine	Lactose	8	IL-6, CRP	No significant change in CRP or IL-6	5
12.2 Rafraf, M. 2015 Iran 28	Healthy obese women *N* = 22 F = 22	Age: 34.40 ± 5.48 BMI: 33.99 ± 2.33	Randomized, double-blind, placebo-controlled study	2 g/day L-carnitine + aerobic training	Lactose + aerobic training	8	IL-6, CRP	IL-6 reduced in both groups, but CRP reduced in intervention group only. No changes in between-group comparison for either variable	5
13 Shakeri, A. 2010 Iran 15	Hemodialysis patients with Lp (a) hyperlipoproteinemia *N* = 36 M = 23 F = 13	Age: 54.5 ± 19.0 BMI: N/M	Unblinded, randomized clinical trial	1000 mg/day oral L-carnitine	Not mentioned	12	IL-6, CRP, TNF-α	CRP reduced significantly, but no significant change in IL-6 or TNF-α	6

TNF-α tumor necrosis factor-alpha, *CRP* C-reactive protein, *IL-6* interleukin-6, *BMI* body mass index, *M* male, *F* female, *N/M* not mentioned

cells [16, 17]. A recent in vitro study has shown that LC might mitigate inflammation by controlling TNF-α and nuclear factor-kappa B (NF-κB) production [17].

There are many randomized clinical trials (RCTs) on the effects of oral and intravenous administration of LC among adult healthy and unhealthy populations, as well as its effects on inflammatory mediators, but their results are inconsistent. Some RCTs suggested that oral LC has a lowering effect on inflammatory mediators, while a few of them did not indicate any effect. However, a meta-analysis in 2015 on six RCTs suggested a lowering effect of LC on CRP [18]. In this meta-analysis, other important inflammatory mediators such as IL-6 and TNF-α were not included, while several new RCTs are available which have either used higher doses of LC or prescribed it for longer duration. Therefore, since there is no systematic review assessing the effect of oral intake of LC on IL-6 and TNF-α in humans, we aimed to perform a systematic review to summarize the effect of oral LC on these inflammatory mediators among healthy and unhealthy adult populations and update its effect on CRP using new published articles in this regard.

Materials and methods

We used systematic search options to search electronic databases including ISI Web of Science, Google Scholar, PubMed/Medline, and SCOPUS to find articles measuring the effect of LC on inflammatory mediators up to October 2018. To search electronic databases, the following MeSH and non-MeSH key words were used: 'TNF alpha', 'Tumor Necrosis Factor-alpha', 'Tumor Necrosis Factor alpha', 'TNF-alpha', 'Tumor Necrosis Factor', 'C-Reactive Protein', 'Protein, C-Reactive', 'C Reactive Protein', 'CRP', 'Interleukin 6', 'IL6', 'IL-6', 'Interleukin-6', 'carnitine', 'L-carnitine', 'Acetyl Carnitine', 'Carnitine, Acetyl', 'acetyl-L-carnitine', 'propionyl-L-carnitine'. To design a systematic search strategy, quotation marks, parentheses, asterisks, and Boolean operators were used. We used quotation marks to search for the exact term, parentheses to search for a group search term, and asterisks to search for all words derived from one keyword. EndNote software (reference manager software, version X6) was used to import all articles found by systematic search method and to read titles and abstracts. Two authors (MH, FH) read titles and abstracts separately, and all discrepancies were resolved by group discussion. In addition, a list of references of relevant RCTs was searched to find additional articles. We did not impose any restriction on publication date or study design. We emailed corresponding authors in cases of any unclear data. The protocol was registered with PROSPERO (No. CRD42019116695).

Inclusion criteria

Articles with the following criteria were considered in the meta-analysis: 1) original articles; 2) articles with randomized controlled trial design; 3) human studies; 4) use of LC for intervention; 5) taking LC in oral form; 6) not taking any other food supplement in intervention or control groups; 7) if LC group had received any intervention alongside LC supplements, that intervention was also received in the placebo group; 8) articles which assessed CRP or IL-6 or TNF-α as the outcome variables; 9) articles that clearly reported the concentration of CRP or IL-6 or TNF-α at the beginning and end of intervention; and 10) English language articles.

Exclusion criteria

Articles with the following criteria were excluded: 1) reporting unclear data in figures and tables; 2) lack of clear inclusion and exclusion criteria; 3) not having control group; 4) taking other food supplements or diet alongside LC in the intervention group but not in the control group; 5) using intravenous form of LC; and 6) recruiting subjects with inflammatory diseases such as arthritis, hepatitis C, or inflammatory bowel disease.

Data extraction

Two authors (MH and FH) assessed eligible articles in order to extract the following information: 1) first author's last name; 2) country in which study was performed; 3) publication year; 4) study design (parallel or cross-over); 5) number of participants in control and intervention groups; 6) mean and standard deviation of IL-6, TNF-α, and CRP; 7) age; 8) body mass index (BMI); 9) health status; 10) LC dose; 11) type of placebo; and 12) study duration.

Quality assessment

A Delphi checklist was used for assessing the quality of articles [19]. Delphi scores range from zero (very poor) to 9 (rigorous) where the included items are: I) standard randomization; II) blinding the participants; III) blinding the researchers; IV) blinding outcome analyzer; V) defining inclusion and exclusion criteria; VI) concealment of intervention allocation; VII) similarity between participants in placebo and intervention group at the beginning; VIII) intention-to-treat analysis; and IX) presenting variability of the outcome.

Statistical analysis

In this meta-analysis, the weighted mean differences (WMD) with standard errors (SE) were used to pool data. WMD was calculated by subtracting change-

from-baseline mean values in the control group from change-from-baseline mean values in the intervention group in each study. To identify the heterogeneity among studies, the I^2 statistic was employed. When I^2 was >50%, the heterogeneity was considered to be statistically significant. In the presence of considerable heterogeneity, random-effects model was used to estimate the pooled effect of treatment; otherwise, a fixed effect model was utilized. Subgroup analysis was also performed to identify the potential sources of heterogeneity. Sensitivity analysis was conducted to assess the robustness of our findings by removing one study at a time. Publication bias was evaluated by Egger's test and visual inspection of funnel plots when the effect sizes were greater than 10. $P < 0.1$ for Egger's test presents a significant publication bias. In the case of bias, trim and fill analysis was conducted to detect the contribution of the bias to the overall effect. All statistical analyses were performed using STATA version 11 software (StataCorp, College Station, TX, USA).

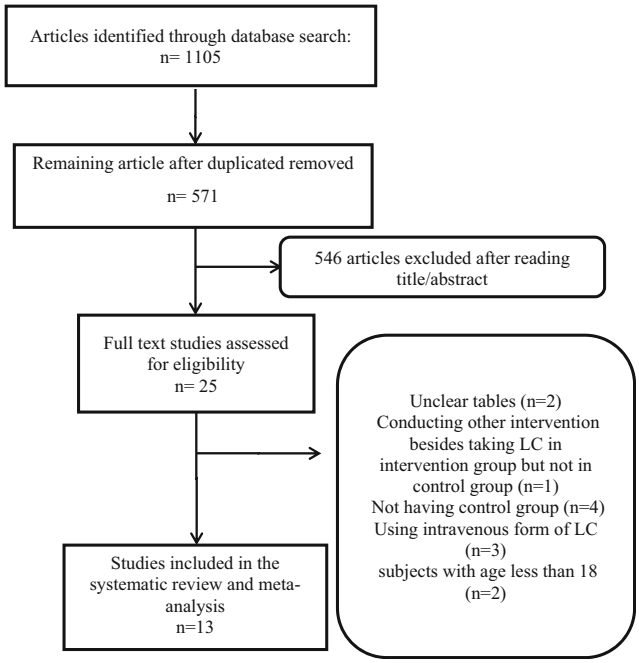

Fig. 1 Flow chart of the study selection

Results

A search of the above-mentioned electronic databases yielded 1105 articles. After removing duplicate articles, 571 remained. Through reading the title and abstract, 546 articles were deleted and 25 articles were assessed for consideration of inclusion or exclusion criteria. According to our inclusion and exclusion criteria, 12 articles were excluded, while 13 articles [12–15, 20–28] were included in our systematic review and meta-analysis (Table 1). Exclusion was for the following reasons (for 17 articles): not having control group ($n = 4$), unclear tables ($n = 2$), conducting other interventions alongside taking LC in the intervention group but not the in control group ($n = 1$), using intravenous form of LC ($n = 3$), subjects younger than 18 years ($n = 2$) (Fig. 1). A total of 1108 participants were included in the present analysis. LC dose ranged from 1500 mg to 4000 mg, and intervention duration ranged from 5 days to 48 weeks. Both men and women were included in all but three articles: one included only men [14] and two only women [12, 28]. We did not include unpublished data in this meta-analysis; no additional information obtained by contacting authors is included in this manuscript.

In a study by Rafraf [28], there were three intervention groups (LC, LC + aerobic training, aerobic training + placebo) and one placebo group. We considered the result of the LC and placebo groups as one study and the result of the LC + aerobic training and placebo + aerobic training groups as another study.

Overall, 10 articles measured CRP [12, 14, 15, 21–23, 25, 27–29], four articles measured IL-6 [14, 15, 20, 28], and seven articles measured TNF-α [13–15, 20, 24, 26, 27].

Findings from the meta-analysis

Nine studies involving 11 comparisons with 455 subjects in the intervention group and 446 subjects in the control group assessed the effect of L-carnitine supplementation on serum CRP levels (Fig. 2). L-carnitine supplementation was significantly associated with lower levels of CRP as compared to the control group (WMD = −1.23 mg/L; 95% CI: −1.73, −0.72 mg/L; $P < 0.0001$). Significant heterogeneity was found among included studies ($I^2 = 95.0\%$). Although subgroup analysis identified L-carnitine dosage and gender as potential sources of heterogeneity (P between subgroups <0.05), none of them could eliminate heterogeneity (Table 2).

Five comparisons from four studies with 86 subjects in the intervention group and 83 subjects in the control group reported the effect of L-carnitine on serum IL-6 changes (Fig. 3). The pooled effect demonstrated a slight but statistically significant decline in IL-6 levels following L-carnitine supplementation (WMD = −0.85 pg/dL; 95% CI: −1.38, −0.32 pg/dL; $P = 0.002$) with significant heterogeneity among included studies ($I^2 = 77.9\%$). Subgroup analysis based on L-carnitine dosage and study duration could not explain heterogeneity (Table 2).

Seven comparisons from six studies including 337 subjects in the intervention group and 335 subjects in the control group measured serum changes in TNF-α following L-carnitine supplementation (Fig. 4). L-carnitine slightly reduced TNF-α concentrations significantly in comparison with the control group (WMD = −0.37 pg/dL; 95% CI: −0.68, −0.06 pg/dL; $P = 0.018$). Significant heterogeneity was observed among the

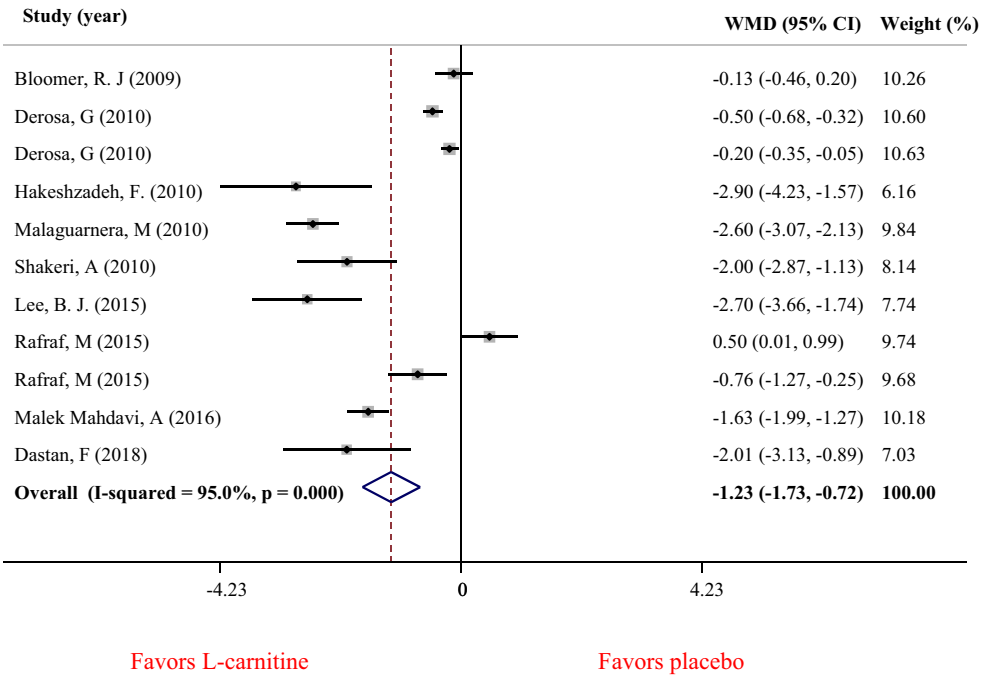

Fig. 2 Forest plot of the effect of L-carnitine supplementation on serum CRP. WMD: weighted mean difference; CI: confidence interval

studies ($I^2 = 91.3\%$). Subgroup analysis based on L-carnitine dosage and study duration could not explain heterogeneity (Table 2), though study duration was identified as a potential source of heterogeneity (P between subgroups < 0.05).

Sensitivity analysis and publication bias

Sensitivity analysis was conducted to determine whether the effect size of any individual trial would alter the pooled effect size. No significant change was observed in the overall effects of L-carnitine on CRP and IL-6, but results for TNF-α revealed that removal of different studies led to non-significant changes in TNF-α levels [13, 14, 27, 29]. Both funnel plot and Egger's regression test suggested evidence of publication bias ($P < 0.1$). However, based on the trim and fill algorithm, the adjusted value did not differ considerably from unadjusted values (WMD = −1.23, 95% CI: −1.73, −0.72). In spite of visual asymmetry in the funnel plot of TNF-α, Egger's regression test suggested no evidence of publication bias ($P = 0.560$).

Discussion

This meta-analysis measured the effect of LC on inflammatory mediators. The results revealed that LC decreased IL-6, TNF-α, and CRP. According to our subgroup analysis, LC was more effective in reducing inflammation in studies with a duration of more than 12 weeks. Furthermore, LC with a dose greater than 2000 mg/day was more effective in TNF-α reduction. Our systematic search method indicated that our meta-analysis is the first article summarizing the effects of LC on IL-6 and TNF-α. On the other hand, one meta-analysis on six articles assessed the LC effect on CRP in 2015. Our meta-analysis confirms the results of Sahebkar's meta-analysis regarding the effects of LC on CRP [18].

Recent evidence has indicated that LC prevents oxidative damage in conditions such as cardiovascular disease by reducing lipid peroxidation, increasing antioxidant defense systems such as antioxidant enzymes, and chelating transition metal ions [30–32]. It is well known that reactive oxygen species (ROS) enhance inflammation [33–35]. ROS can increase the expression of pro-inflammatory mediators and then up-regulate the NF-κB pathway [36]. NF-κB is a transcription factor and regulates the expression of numerous genes involved in inflammatory and immune responses [37].

Furthermore, LC was able to up-regulate peroxisome proliferator-activated receptor (PPAR)γ [38], which is a key factor in the regulation of oxidative stress and liver inflammation [39, 40]. This evidence suggests that LC might be able to improve liver inflammatory response through regulation of CPT I-dependent PPARγ signaling pathway.

Our results indicated that LC at doses higher than 2000 mg/day was more effective in inflammation reduction. Other meta-analysis articles also indicated that LC with a dose greater than 2000 mg/day is more effective in improving health outcomes [41, 42]. New evidence suggests that lower doses of LC are unlikely to provide absorbable levels of carnitine sufficient to have a beneficial effect. Pharmacokinetic studies have reported that LC has poor oral bioavailability and that with a single oral dose of LC, only 5–16% is absorbed; therefore, higher doses might be more effective [43, 44]. According

Table 2 Subgroup analysis for the effect of L-carnitine on serum inflammatory biomarkers

	No. of effect sizes	Mean difference	95% confidence interval	I^2	*P* heterogeneity within group	*P* heterogeneity between groups
CRP						
Sex						<0.0001
Female	3	−0.64	−1.90, 0.62	95.7	<0.0001	
Male	1	−2.70	−3.66, −1.74	–	–	
Both	7	−1.30	−1.90, −0.70	95.3	<0.0001	
Duration						0.358
<12 weeks	5	−0.75	−1.60, 0.10	93.8	<0.0001	
≥12 weeks	6	−1.67	−2.41, −0.94	96.3	<0.0001	
L-carnitine dosage						<0.0001
<2000 mg/day	5	−2.27	−2.84, −1.71	71.0	0.008	
≥2000 mg/day	6	−0.34	−0.65, −0.02	83.2	<0.0001	
IL-6						
Sex						<0.0001
Female	2	−0.37	−0.79, 0.04	33.5	0.220	
Male	1	−0.60	−0.78, −0.42	–	–	
Both	2	−2.76	−3.91, −1.62	0.0	0.397	
Duration						0.225
<12 weeks	3	−0.63	−1.31, 0.05	65.1	0.057	
≥12 weeks	2	−1.78	−4.32, 0.75	90.9	0.001	
L-carnitine dosage						0.108
<2000 mg/day	3	−1.87	−3.67, −0.08	85.8	0.001	
≥2000 mg/day	2	−0.37	−0.79, 0.04	33.5	0.220	
TNF-α						
Sex						0.004
Male	1	−0.80	−1.13, −0.47	–	–	
Both	6	−0.29	−0.63, 0.05	91.7	<0.0001	
Duration						<0.0001
<12 weeks	5	−0.16	−0.59, 0.28	81.7	<0.0001	
≥12 weeks	2	−0.70	−1.09, −0.31	88.5	<0.0001	
L-carnitine dosage						0.741
<2000 mg/day	3	−0.03	−0.96, 0.89	90.9	<0.0001	
≥2000 mg/day	4	−0.55	−0.93, −0.18	93.6	<0.0001	

to our subgroup analysis, LC was more protective in studies longer than 12 weeks. A meta-analysis demonstrated that taking LC for longer periods is more effective in LDL-c reduction [45]; therefore, by reducing atherogenic factors, LC might decrease inflammatory mediators.

There is new evidence regarding the effect of LC on health outcomes such as glucose metabolism and lipid profile [46, 47]. Two recent meta-analyses indicated that LC could improve insulin resistance [46, 47]. LC might improve the glycemic index by reducing inflammation, especially CRP [48]. High levels of CRP may cause glucose intolerance and insulin resistance [49]; therefore, LC can improve insulin resistance by reducing CRP concentration.

Strengths

For our article, several strengths should be considered: First, our results indicated that LC could decrease inflammatory mediators which are considered risk factors for metabolic diseases; therefore, our results will help inform clinicians regarding a consensus of the effects of LC on metabolic disease risk factors. Second, we did not impose any limitation on publication time or article language. Further, we indicated the effects of sex, LC dose, and intervention duration on the effect of LC on inflammatory mediators by subgroup analysis. Also, systematic search results indicated that this meta-analysis is the first to examine the effects of LC on inflammatory mediators.

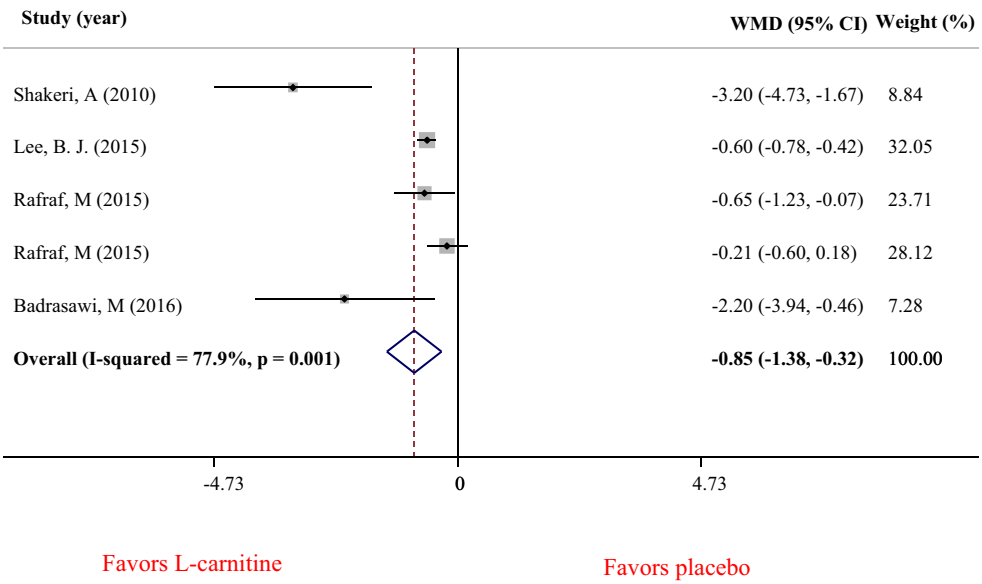

Fig. 3 Forest plot of the effect of L-carnitine supplementation on serum IL-6. WMD: weighted mean difference; CI: confidence interval

Next, we excluded studies which used nutrients other than LC in the intervention group, and we could therefore exclude the confounding effects of other nutrients. Finally, lack of significant asymmetry in funnel plots was evidence of no publication bias.

Limitations

The following can be considered as limitations of this meta-analysis: 1) The most important limitation was the small number of studies included in the quantitative data synthesis. We had five effect sizes for IL-6, 11 effect sizes for CRP, and seven effect sizes for TNF-α. 2) Our meta-analysis could not identify any correlation between the reduction in inflammatory mediator levels and participants' clinical outcomes. 3) Since changes in body composition can influence the concentration of inflammatory mediators, subgroup analysis based on changes in fat mass and fat-free mass would be more informative, but most articles did not include information related to changes in body composition. 4) Heterogeneity was high in our analysis. 5) Articles conducted separately on men and women were limited; therefore, gender differences in the effect of LC on inflammation remain unknown. 6) Some confounding factors such as dietary intake of participants, smoking, and physical activity were not considered in the analysis, as no article had information related to them. 7)

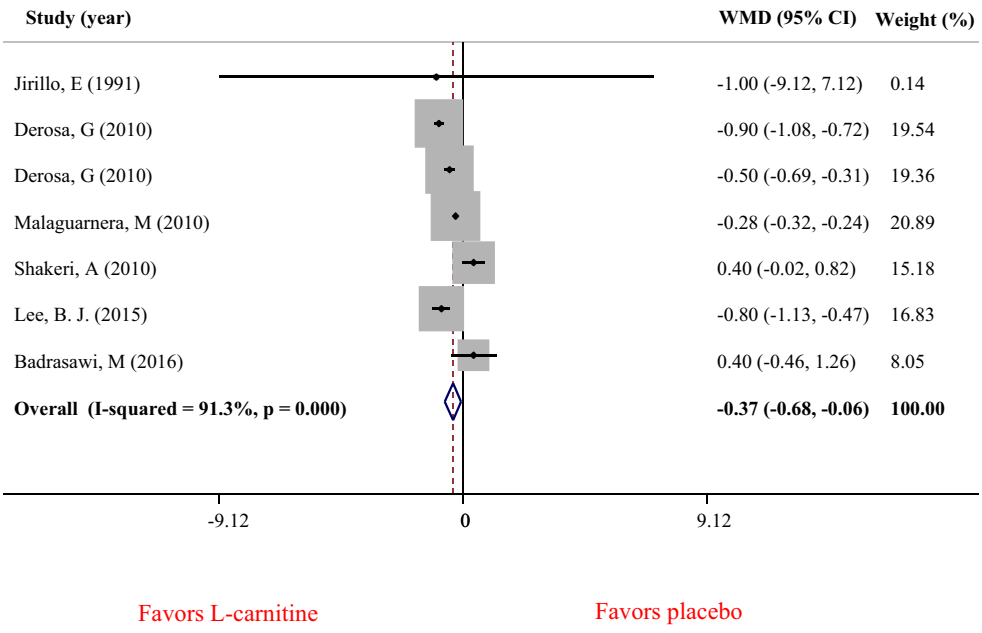

Fig. 4 Forest plot of the effect of L-carnitine supplementation on serum TNF-α. WMD: weighted mean difference; CI: confidence interval

There was considerable heterogeneity among studies, and we could not eliminate it by statistical methods. Therefore, the results of this meta-analysis should be interpreted with caution.

Conclusion

In conclusion, our results indicate that LC reduced inflammatory mediators, especially in studies with a duration of more than 12 weeks. Additional studies with different doses and intervention duration, and separately on men and women, are necessary. Changes in body composition, nutrient intake, physical activity, and smoking should be considered as confounding factors in future studies. Since inflammatory markers are surrogate parameters, future studies should indicate whether reducing inflammation is associated with improved clinical outcomes.

Author contributions **MH** found keywords and conducted database searches. **FH, MH, and MJ** found relevant RCTs, excluded irrelevant RCTs, read full text of articles, and extracted data. **FH** conducted statistical analysis. **MH** wrote the first version of article, **FH** corrected the first version of the paper, and **MJ** performed final editing. Discrepancies in any part of the work were resolved through group discussions. **MJ** rewrote some parts of the manuscript according to reviewers' comments.

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