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Research Article

Can L-Carnitine Replace Tumor Necrosis Factor-Alpha Blockers? A Systematic Review and Dose–Response Meta-Analysis

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Abstract

Background: L-carnitine (LC), an amino acid-like molecule, has been shown to reduce tumor necrosis factor-alpha (TNF-α), although some research has not confirmed its impact. This study aimed to identify the effects of LC supplementation on TNF-α levels through a systematic review and meta-analysis of randomized controlled trials (RCTs).

Methods: This study followed the PRISMA 2020 statement and searched the Web of Science, PubMed, Embase, and Scopus for related papers on LC supplementation's effects on TNF-α in adults. The meta-analysis was performed using the 17th version of the Stata Statistical Software, and the I^2 statistic was used to assess the impact of heterogeneity. The Cochrane risk of bias tool was used to evaluate the risk of bias in the included studies.

Results: Seventeen RCTs were included based on the full-text review, and the data from 14 studies were included in the meta-analysis. Based on the results, oral LC did not have a significant impact on TNF-α levels (Cohen's d: -0.19 [95% CI: -0.71 to 0.33]; I^2: 97.39%). However, parenteral LC had significantly reduced TNF-α levels (Cohen's d: -1.60 [95% CI: -3.06 to -0.15]; I^2: 88.92%). Oral LC doses of 0.75 and 6 g/day were effective, while duration of LC administration was associated with significant findings in 2, 36, and 48 weeks. The dose and duration of LC administration ineffective independently of TNF-α levels ($P = 0.35$ and $P = 0.70$ for dose and duration of administration, respectively).

Discussion: In this meta-analysis, oral LC supplementation failed to be superior to TNF-α blockers.

Introduction

Historically, inflammation has been a complex biological process linked to infection and the immune system. However, recent evidence suggests a much more comprehensive range of diseases are associated with inflammation.[1-3] For instance, non-resolving inflammation plays a key role in the pathogenesis of atherosclerosis, cancer, chronic obstructive pulmonary disease, obesity, asthma, inflammatory bowel disease, rheumatoid arthritis, neurodegenerative disease, depression, and multiple sclerosis.[4,5] Therefore, anti-inflammatory medicines that are effective in a specific inflammatory disease may prove effective in other inflammatory diseases and result in a broad range of intervention options. The prevalence of inflammatory diseases in developed western countries is 5–7% and is gradually increasing.[6] One of the main molecular mediators of chronic inflammation is tumor necrosis factor-alpha (TNF-α).[7] As a result, TNF-α inhibitors such as the circulating receptor fusion protein and monoclonal antibodies have been developed. However, these blockers come with serious side effects and are quite costly.[8] Consequently, there is a need for agents that are cost-benefit, and safe.

L-carnitine (LC), or L-β-hydroxy-γ-N-trimethylaminobutyric acid, is an amino acid-like molecule that is mainly used as a dietary supplement for several health indications.[9] LC is mainly synthesized in the kidneys and liver.[10] The essential role of LC is to transfer fatty acids into the mitochondrial matrix and make them available for β-oxidation, producing energy via the Krebs cycle.[11]

There are reports of the reduction of circulating TNF-α levels and inhibition of its action by LC according to in vitro and in animal models.[12,13] Some clinical trials have shown reduced levels of TNF-α after LC administration, which suppresses organ inflammation.[14,15] Inversely, the results of several other studies showed that LC administration had no significant effect on the level of this inflammatory

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factor.[16-18]

Although there are several randomized clinical trials (RCTs) to assess the effect of oral and intravenous LC on TNF-α, their results are contradictory. Some RCTs have suggested that LC has a reducing effect on reduces TNF-α, while others did not report any effect. However, the latest meta-analysis of 48 RCTs suggested a decreasing effect of LC on TNF-α.[19] This meta-analysis did not include new RCTs. Furthermore, this study mistakenly included an article that did not have TNF-α in its evaluated outcomes,[20] which seems to affect the final result. Finally, due to equivocal results of the most recent meta-analysis and the increasing prevalence of inflammatory diseases, we decided to investigate how LC influences TNF-α and compare the optimal oral and intravenous (IV) LC to healthy and unhealthy adults.

Methods

The preparation of this systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21]

Eligibility criteria

Inclusion and exclusion criteria for selection of studies were listed in Table 1.

Information sources and search strategy

Two researchers (F.N. and A.N.) comprehensively searched the Web of Science, Scopus, Embase, and PubMed on December 31, 2023. Additionally, specific relevant papers and websites were manually searched. The reference lists of the chosen papers were evaluated. To find additional information about the related studies, the reference lists of the chosen articles and relevant review articles were manually searched. The database search results were imported into the Endnote X20 citation manager program for further analysis. After endnote software eliminated duplicate studies, the remaining papers were manually reviewed for duplication. Searches were performed using the keywords tumor necrosis factor, carnitine, l-carnitine, levocarnitine, vitamin b and other similar keywords. The search strategy in each database is detailed in supplementary data.

Selection process

The database search results were imported into the Endnote 20 citation manager program for further analysis. After endnote software eliminated duplicate studies, the remaining papers were manually reviewed for duplication. After removing duplicates, articles were selected by screening the title and abstract of the imported studies (F.N. and A.N.), and unrelated articles were removed. Two independent reviewers (F.N. and A.N.) thoroughly assessed the full text of the remaining studies. Any disagreements were resolved by another reviewer (S.S.[1]), and the consensus was achieved in all cases.

Data collection process and data items

The data extraction table includes the name of the first author of the study, publication year, study design, sample size, age, BMI, underlying condition, LC dose, route of administration, follow-up duration, main results (consisting of TNF-α levels before and after administration of LC and placebo), and conclusion of the study. Two researchers (F.N. and A.N.) extracted the data, and two additional reviewers (A.GH. and S.S.[1]) examined and verified the accuracy of the extracted data. Disagreements were resolved by another reviewer (S.S.[2]), and in all cases, consensus was achieved.

Study risk of bias assessment and certainty of the evidence

We assessed the potential for bias in the estimates of the impact of assignment to the intervention (intention-to-treat) for all outcomes via the Cochrane risk of bias tool (RoB2).[22] Potential bias was identified in five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Additionally, an assessment of the overall risk of bias was performed. The risk of bias for each domain and the overall risk of bias were categorized as "low," "some concerns," or "high." Two reviewers (F.N., A.N.) conducted this stage independently. Reviewers' discrepancies were handled through discussion and, if consensus could not be achieved, by a third reviewer (S.S.[2]). Finally, the certainty of the evidence was assessed using the Cochrane GRADE approach.[23]

Synthesis methods of results

The meta-analysis was conducted using the 17th version of the Stata Statistical Software (College Station, TX: StataCorp LLC.). The I^2 statistic was used to quantify the effect of heterogeneity. A random-effect model was applied due to the considerable heterogeneity between the studies.

Table 1. Inclusion and exclusion criteria for selection of studies.

Inclusion Criteria	Exclusion Criteria
• Population: Adult patients whose inflammation plays a role in the pathophysiology of their disease.	• Articles published in non-English language
• Intervention: L-carnitine administration in any rout, alone or together with other agents	• Non- randomized clinical trials, conference presentations, case reports, case series, and letters to the editor
• Comparison: Placebo or other agent	• Community-based articles
• Outcome: tumor necrosis factor-alpha	• Animal studies
• Study design: randomized clinical trials	

The mean and standard deviation (SD) before and after the intervention for the LC and control groups were utilized to calculate the effect size. The SD change was calculated using the following equation.[24]

$$SD\,change = \sqrt{SD\,before^2 + SD\,after^2 - 2 * r * SD\,before * SD\,after} \qquad \text{Eq.(1)}$$

Also, subgroup analyses based on g/day of LC usage and duration of treatment were conducted. Furthermore, 95% confidence intervals (CIs) and a 0.05 level of significance were observed in all the statistics. Meta-regression was performed based on grams per day and the duration of LC administration in weeks. The possibility of publication bias was assessed using Egger's test and presented by funnel plot.

Results

Study selection

Figure 1 illustrates the flow of articles through the search process. The search yielded 3643 studies. After deduplication, 1739 studies remained, and the initial screening phases provided us with 39 to evaluate. Finally, 17 RCTs were included in this systematic review according to the inclusion and exclusion criteria.

Study characteristics

From a total of 17 RCTs, four took place in Iran,[14,18,25,26] six in Italy,[15,17,27-30] two in China,[16,31] one in Taiwan,[32] one in Egypt,[33] one in Malaysia,[34] one in Poland,[35] and one in the United States.[36] Ten RCTs were double-blinded,[14,15,17,25,26,29,30,34-36] two was were single-blinded,[31,32] two open-label RCTs,[16,18] and three studies had unknown blinding.[28,33,37] A total of 1185 individuals were included and the sample size ranged from 20[17,28] to 258.[30] The mean number of patients among the studies was 69.71and the mean follow-up duration was 14.55 weeks with a maximum and minimum of one day to 48 weeks. In terms of supplementation, various substances were used in each study. Ten studies used LC as their only intervention.[14,17,18,25,26,32,35,36] Except for three studies in which parenteral LC was administered,[16,28,31] LC was administered orally in the rest. The population of the studies was immensely heterogeneous. Table S1 in supplementary data shows a brief overview of the characteristics of the included studies.

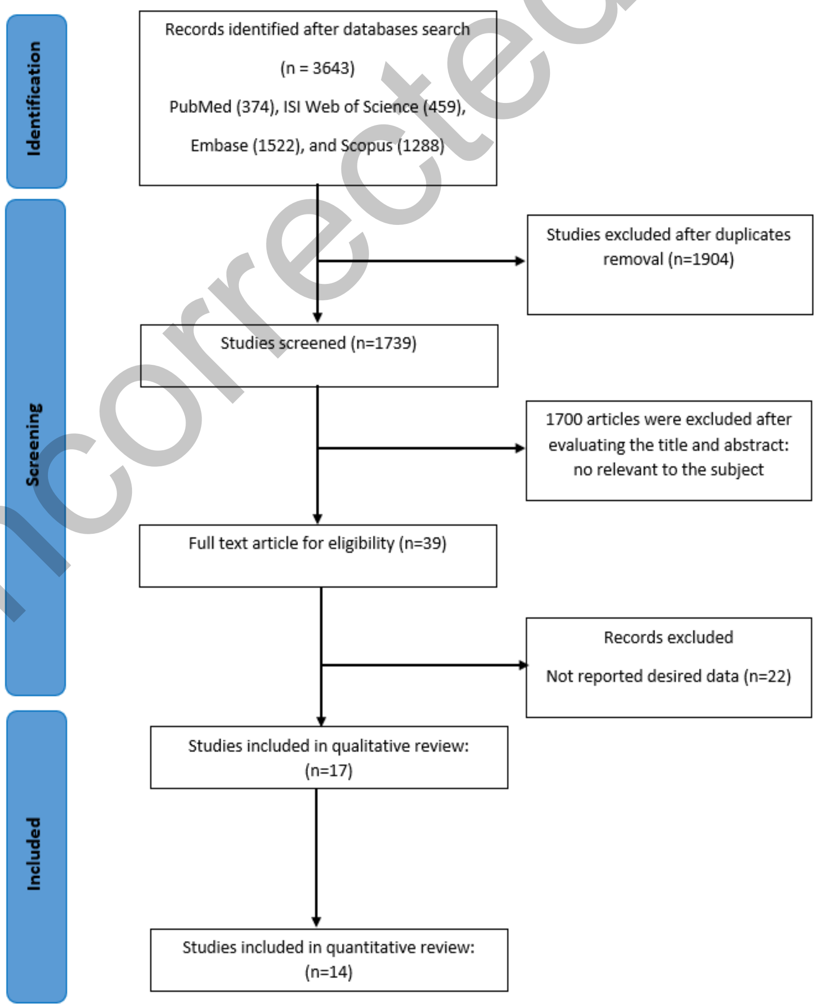

Figure 1. PRISMA flow diagram.

Risk of bias in studies

The quality of the included studies was assessed using version 2 of the Cochrane risk-of-bias tool for randomized trials (Figure 2). Accordingly, three studies were considered high-risk,[15,25,37] and the rest owere evaluated as "some concern."[14,16-18,26,28-36] One study (24%) had a high risk of bias in the randomization process. Six studies (24%) had an unclear risk of bias for random sequence generation. For allocation concealment, eight studies (32%) had an unclear risk of bias. Blinding of the participant was unclear in two studies (8%), blinding of outcome assessment was high risk in one study (4%), and unclear in two studies (8%). Regarding attrition bias, all the RCTs had low risks of bias. High and unclear reporting bias was detected in thirteen (52%) and seven (28%) studies, respectively.

Results of the synthesis

The results of the meta-analysis are presented in Figure 3. Based on the quantitative synthesis, LC did not seem to have a considerable effect on TNF-α levels (Cohen's d: -0.32 [95% CI: -0.83 to 0.20]; I^2: 97.39%).

Subgroup analyses based on the route of LC administration showed that the impacts of IV and oral LC are different from each other. So in the subsequent analysis, we included only RCTs with oral LC administration. Oral LC did not significantly reduce TNF-α levels (Cohen's d: -0.19 [95% CI: -0.71 to 0.33]; I^2: 97.39%). However, IV LC was associated with a significant reduction in its levels (Cohen's d: -1.60 [95% CI: -3.06 to -0.15]; I^2: 88.92%) (supplementary data).

In subgroup analyses based on the dose of oral LC, we found only 0.75 and 6 g/day dosage as effective (Figure 4). In addition, the results of subgroup analyses based on the duration of LC usage in weeks were associated with significant findings in 2, 36, and 48 weeks (Figure 5).

According to the meta-regression, which was

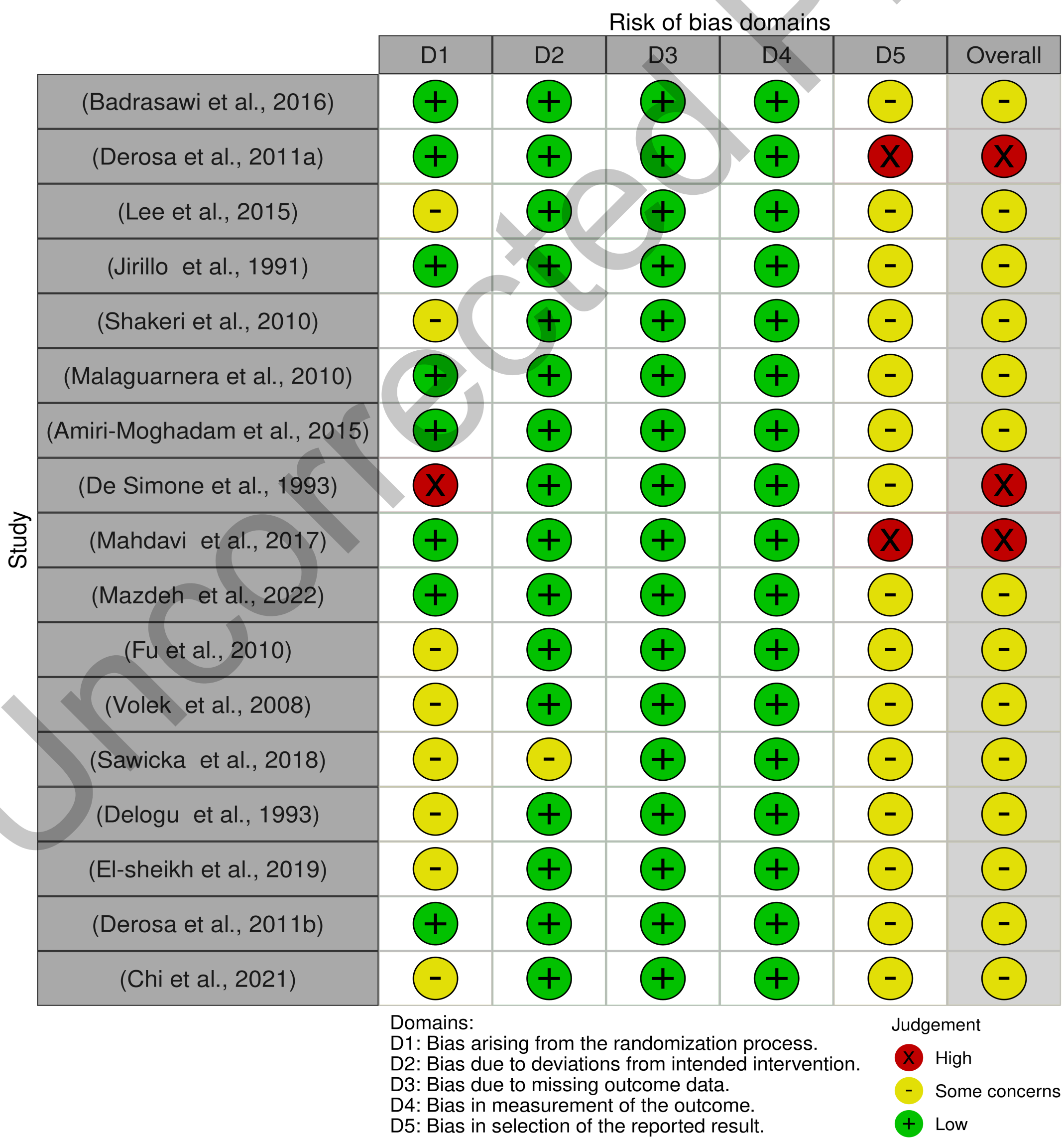

Figure 2. The risk of the bias assessment of the included studies according to the Cochrane guidelines.

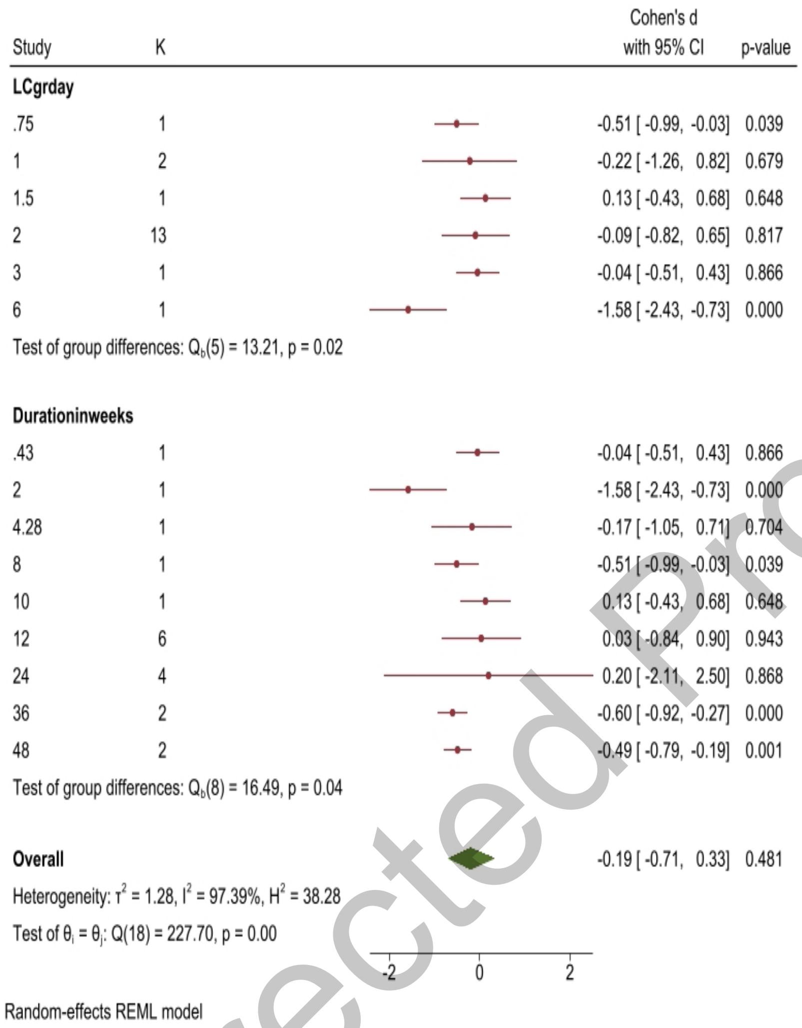

Figure 3. The results of meta-analysis based on dose of oral L-carnitine administration in grams/day.

performed based on grams per day and the duration of LC administration, none of them were effective independent of TNF-α levels (*P = 0.35*, *P = 0.70* for dose and duration of administration, respectively). The highest significant decrease in the TNF-α levels is 6 g/day for two weeks (Figure 6).

Meanwhile, the subgroup analysis was carried out based on country, revealing that the differences between countries may influence the results (*P = 0.00*). The subgroup analysis showed that in Egypt, Italy, and Iran, the reduction of TNF-α levels after LC supplementation is statistically significant (*P = 0.002*, *P = 0.00*, and *P = 0.001*, respectively) (supplementary data).

Publication bias

Figure 7 presents the funnel plot for the meta-analysis. There was no significant publication bias based on our assessments using Egger's test (p-value: 0.43) and Begg's test (p-value: 0.78) for minor study effects in the meta-analysis.

Certainty of evidence

All studies were RCTs; however, considering the concerns regarding the risk of bias, significant level of heterogeneity, and imprecision of results due to small sample sizes, the level of evidence for the effects of LC on TNF- α was moderate.

Discussion

In this meta-analysis, we evaluated the impact of LC administration on TNF-α levels. Our findings revealed that oral LC supplementation did not significantly decrease TNF-α levels. However, IV administration reduced its levels significantly. Subgroup analyses based on oral LC dose revealed that only 0.75 and 6 g/day efficiently reduced TNF-α levels. Furthermore, subgroup analyses based on the duration of LC administration in weeks yielded significant outcomes in 2, 36, and 48 weeks. According to the meta-regression, which was based on grams per day and the duration of LC supplementation, we found that none of them were effective on TNF-α levels independently. In the meantime, the country-based subgroup analysis showed

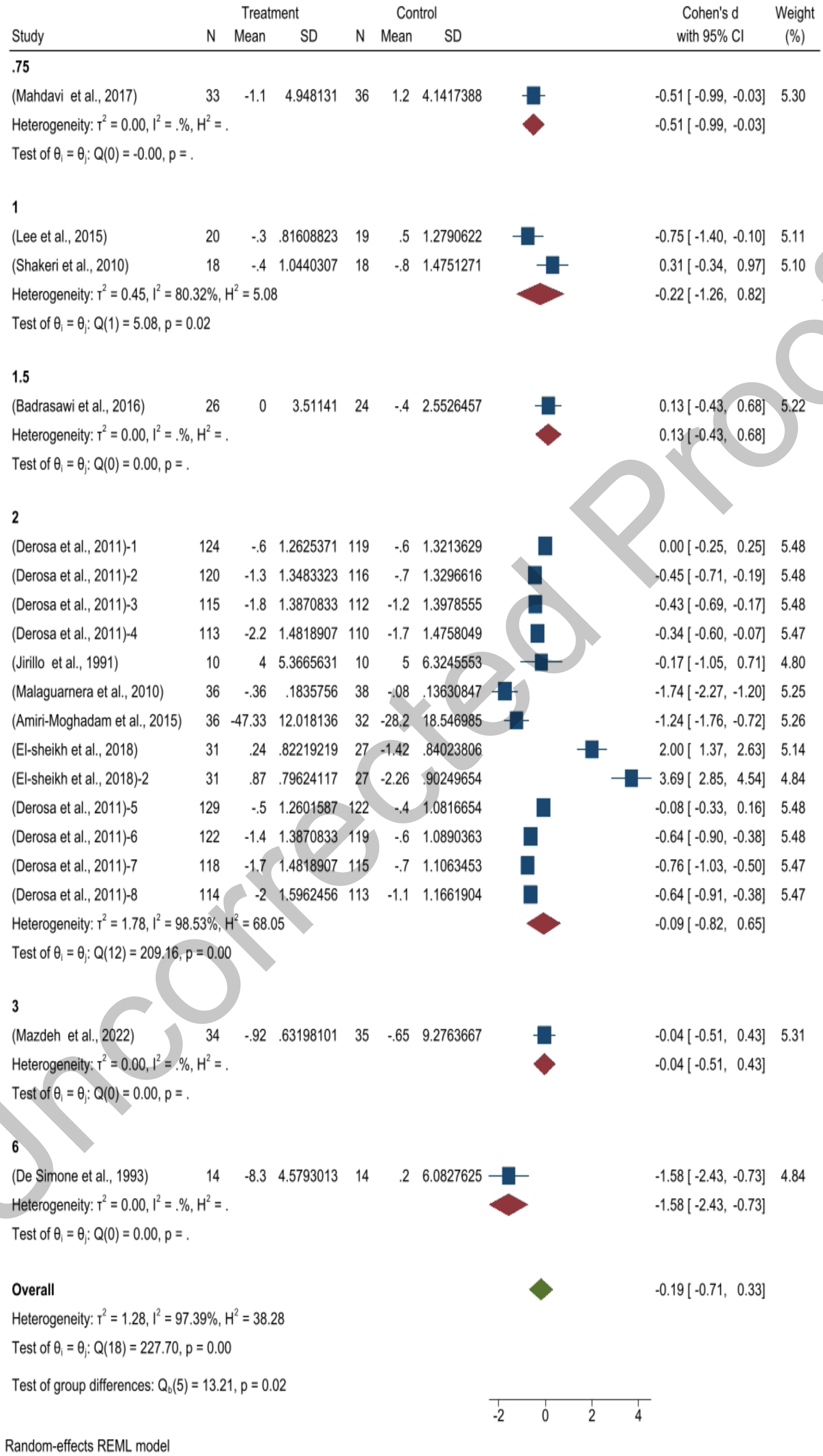

Figure 4. The results of meta-analysis based on dose of oral L-carnitine administration in grams/day.

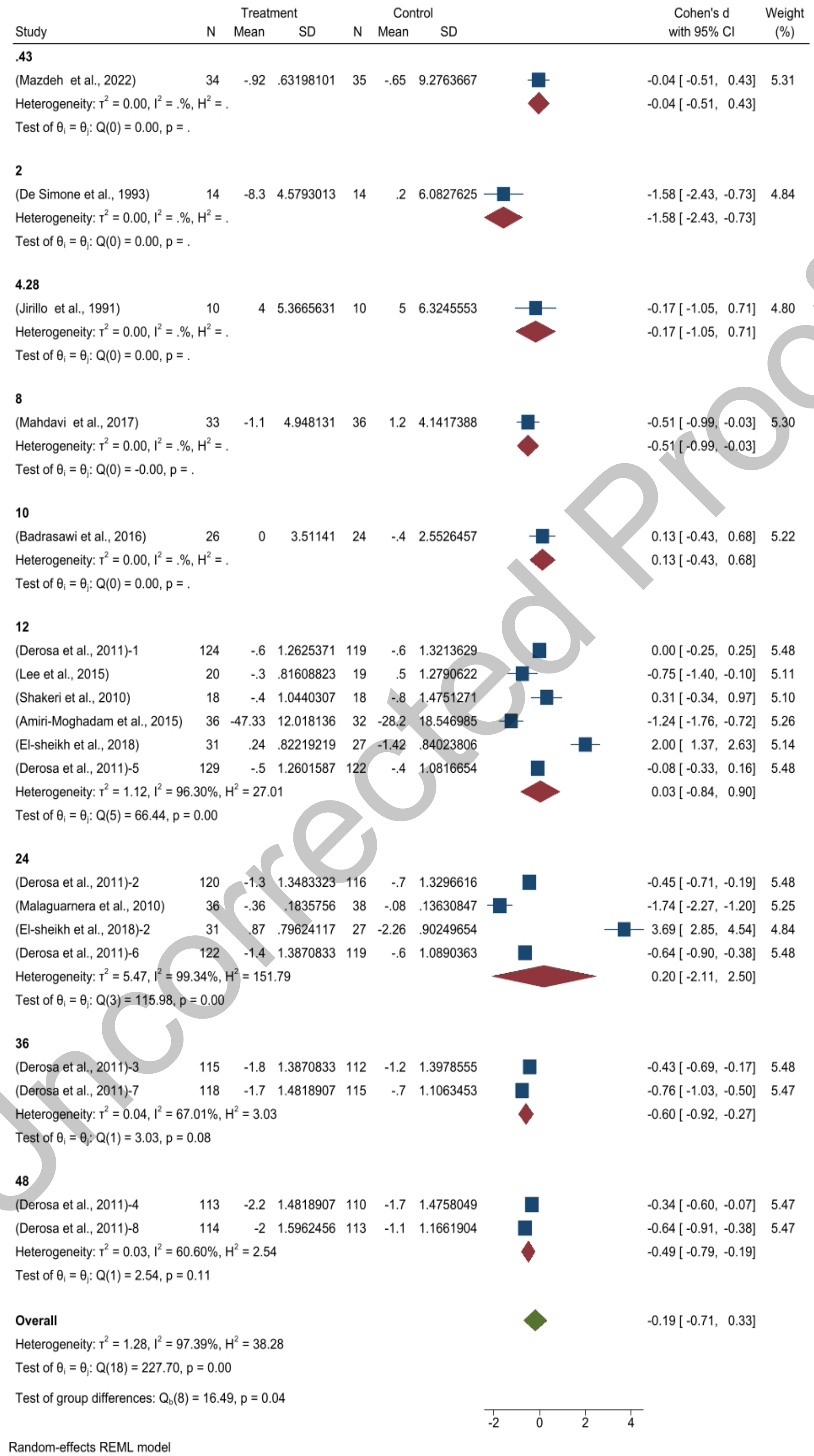

Figure 5. The results of meta-analysis based on the duration of oral L-carnitine administration in weeks.

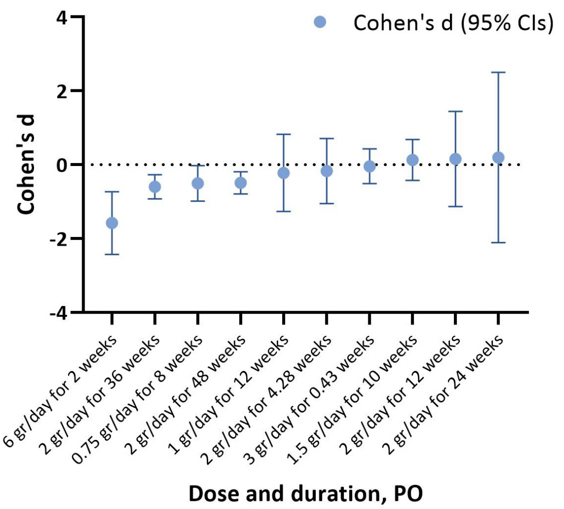

Figure 6. The results of meta-regression based on dose of oral L-carnitine in grams/day and the duration administration in weeks.

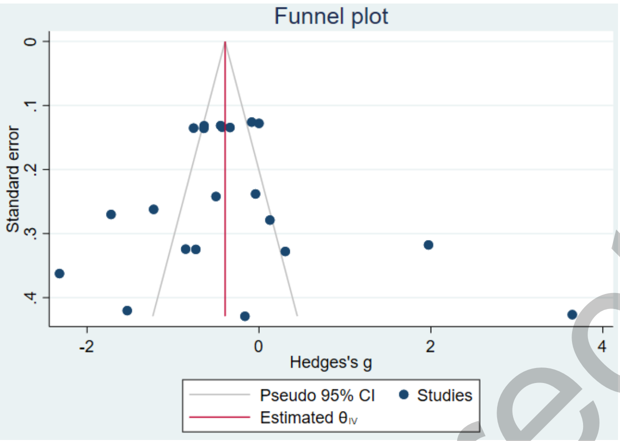

Figure 7. Funnel plot detailing publication bias in the studies reporting the impact of L-carnitine on plasma TNF-α concentrations.

that the variations among countries might impact TNF-α levels.

The US FDA has approved TNF-α blockers, such as adalimumab, etanercept, and infliximab, for the treatment of treating several inflammatory chronic diseases. However, they have a long list of serious severe side effects, such as pancytopenia, thrombocytopenia, leukopenia, neutropenia, and liver damage.[38] Thus, it would appear that safer alternatives are required. This meta-analysis assessed LC's impact on TNF-α as a potential safer alternative. From the pathophysiological point of view, nuclear factor kappa B (NF-κB) is a transcription factor that regulates the immune system's functions and inflammatory cascades. It induces pro-inflammatory genes, participates in inflammasome regulation, and plays a critical role in innate immune cell survival and differentiation. Deregulated NF-κB activation contributes to inflammatory diseases.[39] LC inhibits the activation of NF-κB and subsequently prevents the induction of inflammatory cytokines such as TNF-α.[40] In certain studies, LC supplementation significantly decreased TNF-α concentrations compared to a placebo.[15,29,32] Other researchs, failed to identify any significant reduction.[16-18] For example, Sawicka *et al.*[35] could not show any significant effects of LC supplementation at a dosage of 1,500 mg/day for 24 weeks on TNF-α concentration in healthy women older than 65. In another study in hemodialysis patients, IV administration of LC 1 g/day after each hemodialysis session for three months did not change the circulating TNF-α levels.[16] Carnitine is a general term for all kinds of compounds. The most common among them in the body and supplements is L-carnitine. Other analogs include acetyl L-carnitine, propionyl L-carnitine, and L-carnitine L-tartrate. Studies have shown that the bioavailability of carnitine analogs is different from each other. Acetyl L-carnitine is the most bioavailable analog.[41] Perhaps one of the reasons for the significant difference in the results of different studies was the administration of different LC analogues. Another reason can be due to the different disease conditions in the included studies. Also, the influence of the difference in demographic characteristics of patients in the studies cannot be ignored. For example, higher TNF-α concentrations correlated with increasing age[42] and increasing adiposity.[43]

The findings showed that LC did not influence have a significant impact on TNF-α levels significantly. In contrast to our findings, the latest meta-analysis by Rastgoo *et al.*[19] reported a significant decrease in TNF-α levels. Also, the meta-analysis by Haghighatdoost *et al.*[44] showed that oral LC supplementation was linked to a small but statistically significant drop in TNF-α levels (WMD = −0.37 pg/dL; 95% CI: −0.68, −0.06 pg/dL; $P = 0.018$). In addition, another meta-analysis found the same result.[45] Reported meta-analysis by Rastgoo *et al.*[19] was published in 2023 and included ten studies up to October 2022. In comparison, our study identified potentially relevant RCTs in December 2023. Furthermore, in their research, a study by Lee *et al.*[20] has been included, in which TNF-α was not among the study's outcomes. According to our subgroup analysis, LC at a dose of only 0.75 and 6 g/day mg/day was effective in TNF-α level reduction. Furthermore, a significant correlation was found in weeks 2, 36, and 48 between the outcomes of subgroup analyses based on the duration of LC consumption expressed in weeks.

All mammals have LC (3-hydroxy-4-N-trimethylammonial-oxidaum butyrate), an amino acid-like substance. This small molecule constitutes the main portion of the "carnitine pool" in the body. The short-, medium-, and long-chain esters referred to as acyl-carnitine are further components of this pool. The most common analog in plasma and other tissues is acetyl L-carnitine.[46] Patients with chronic diseases are often found to have low serum levels of free carnitine.[47] The patients in the present study also often had chronic diseases, which probably had a low serum level of free carnitine. Maybe the administrated doses of LC in the included studies are inadequate to produce enough levels of carnitine to be beneficial.

Intravenous LC was associated with a significant reduction in its levels. Of course, this result was expected because the bioavailability of oral LC is around 5–16%, which is a minimal amount compared to the 100% bioavailability of the injectable form.[48]

The results of the subgroup analysis based on nation indicated that variations in the country could have an impact on the reduction of TNF-α levels. The reason for this difference in the results between countries can be attributed to the difference in the ethnicity of the participants in the study. Compared to non-Hispanic whites, non-obese Mexican Americans have been found to have higher levels of TNF-α.[49] In response to environmental stressors, genetic and epigenomic factors that affect metabolism and inflammation could primarily explain these variations. For instance, variations in a person's reaction to inflammatory stimuli may significantly affect development of both acute and chronic inflammatory disorders.[50] Another reason could be differences in the resting levels of inflammatory markers between races.[51,52]

For future research, it is recommended that the measurement of inflammatory factors be combined with the measurement of serum carnitine levels to determine whether administering LC at different doses in various populations results in a sufficient increase in serum carnitine levels, effectively reducing the level of inflammatory factors. Another suggestion for future studies is to consider the effect of LC intake through diet. Because the main source of LC intake is the diet,[53] the bioavailability of LC in food is much higher than the bioavailability of its supplemental source (54 -87%[54] versus 5-16%[48]). Therefore, it seems that the effects of LC, received from the diet, on inflammatory factors and serum carnitine levels cannot be ignored.

The strength of the current study is that it is the only study examining the effect of parenteral LC on TNF-α. This study suggests that there might be a few possible limits. The first is the limited number of studies with various populations, which undoubtedly affected our results. The second was the variety of assessment methods and the dosage, route, and duration of LC administration. This produces even more controversial results. Furthermore, we only included published research in Farsi and English in our search. Finally, it was not possible impossible to perform a meta-analysis with subgroup analysis in different populations due to data heterogeneity. There was some concern about bias in almost half of the included studies, which affected the validity of the findings of our meta-analysis and we did not consider the impact of dietary LC consumption.

Conclusion

In conclusion, the present meta-analysis showed that LC did not have significant impact on TNF-α levels, generally. However, unlike oral LC, parenteral LC had significantly reduced TNF-α levels. It seems that to reach a comprehensive conclusion and confirmation of the effects of oral LC on TNF-α, well-designed RCTs, with higher doses and duration of administration, would be helpful.

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Author Contributions

Farnaz Naeimzadeh: Writing - Original Draft, Methodology, Visualization, Writing - Review & Editing. Amirreza Naseri: Methodology, Formal Analysis, Visualization, Writing - Review & Editing. Sarvin Sanaie: Conceptualization, Methodology, Data Curation, Project administration, Writing - Review & Editing. Seiedhadi Saghaleini: Conceptualization, Methodology, Writing - Review & Editing. Afshin Gharekhani: Conceptualization, Methodology, Supervision, Funding acquisition, Writing - Review & Editing.

Conflict of Interest

The authors have not disclosed any competing interests.

Supplementary Data

Supplementary data are available at https://doi.org/10.34172/PS.2024.13.

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