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Does L-carnitine supplementation affect serum levels of enzymes mainly produced by liver? A systematic review and meta-analysis of controlled clinical trials

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ABSTRACT

Background & Aims: L-carnitine supplementation is proposed to be associated with reduced liver enzymes levels; however, previous findings are equivocal. The current systematic review and meta-analysis of controlled clinical trials was performed to assess the effect of L-carnitine supplementation on liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGTP)] levels.

Methods: Online databases, including PubMed, Web of science, Scopus, and Google Scholar, as well as the reference lists of identified relevant studies were searched from database inception up to June 2019. The risk of bias in individual studies was assessed using Cochrane Collaboration's tool. Data were pooled using the random-effects model and expressed as mean differences (MDs) with 95% confidence intervals (CIs).

Results: In total, nineteen trials (1206 participants) met the eligibility criteria. Intervention duration ranged from 2 to 48 weeks and L-carnitine supplementation dose ranged from 500 to 4000 mg/day. L-carnitine supplementation significantly reduced serum ALT (MD = -10.97 IU/L, 95% CI: -16.46, -5.48), AST (MD = -9.03 IU/L, 95% CI: -12.73, -5.33), and GGTP (MD = -7.88 IU/L, 95% CI: -12.11, -3.64) levels. The subgroup analysis showed that L-carnitine might be more effective in reducing liver enzymes with higher doses (≥ 2000 mg/day), longer treatment durations (> 12 weeks), and also among patients with liver diseases.

Conclusion: L-carnitine supplementation significantly improves circulating ALT, AST and GGTP levels; therefore, it might positively affect liver function, especially among patients with liver diseases.

Key words: L-carnitine; alanine aminotransferase (ALT); aspartate aminotransferase (AST); Systematic Review; Meta-Analysis

INTRODUCTION

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which are also known as serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT), respectively, are found in the liver, heart cells, red blood cells, muscle tissue, and other organs, such as the pancreas and kidneys; however they are mainly produced in the liver (1, 2). These enzymes play a key role in transferring the α-amino group from alanine and aspartate, to the α-keto group of ketoglutaric acid to produce pyruvic acid and oxalacetic acid respectively, which are important in gluconeogenesis and amino acid metabolism (3-5). Although measurement of serum ALT and AST levels is primarily used for the diagnosis of hepatic disease, the elevation of aminotransferase levels is not specific to liver disease. AST, which appears in skeletal muscle, the brain, the heart and red blood cells, is less specific for liver damage (6, 7). The concentration of ALT is found to be lower than AST in all cells, except in hepatic cells; therefore, its elevation is particularly related to liver disease (8-10). Gamma-glutamyl transpeptidase (GGTP) is another nonspecific marker of liver disease and also found in other organs; it is a plasma membrane enzyme that can counteract oxidative stress by increasing intracellular glutathione synthesis (11, 12). The consumption of even small amounts of alcohol increases the GGTP levels, and therefore, may be used as a biological marker for acute or chronic alcohol abuse (13, 14).

Several epidemiological associations have been reported between these enzymes, which are regarded as markers of liver dysfunction and type 2 diabetes mellitus (15-17), cardiovascular disease (1, 18-20), and mortality from vascular and non-vascular diseases (21-23). With regard to many conditions which might increase liver enzymes, assessment and treatment should be focused on identifying and eliminating harmful agents, concurrent to applying the appropriate medical therapy and non-pharmacological treatments.

Carnitine (β-hydroxy-γ-N-trimethyl aminobutyric acid), regarded as vitamin BT, is the generic phrase for a number of compounds like L-carnitine, acetyl-L-carnitine, and propinyl-L-carnitine (24, 25). L-carnitine is the active form of carnitine, which is found in the body, food and most dietary supplements (26), and is responsible for the transfer of fatty acids to mitochondria and, consequently, involved in energy production through β-oxidation of fatty acids (27, 28). L-carnitine supplementation has been shown to be beneficial in the prevention or treatment of end-stage kidney disease (29), cardiovascular disease (30), dialysis-related hypertension (31), persistent depressive disorder (32), non-alcoholic fatty liver disease (33), and sarcopenia in patients with liver cirrhosis (34). Recently, it has been proposed that L-carnitine supplementation might be effective in reducing serum liver ALT levels (35-38). Several clinical trials have evaluated the effect of L-carnitine supplementation on the levels of liver enzymes; however, the evidence remains inconclusive. Although a number of studies provide evidence that consuming L-carnitine might be effective in reducing these enzymes (35-38), others demonstrate no significant effect on serum ALT and AST levels (39-44).

To the best of our knowledge, no study has yet attempted to summarize the published evidence regarding the effect of L-carnitine supplementation on serum levels of enzymes mainly produced by the liver. Therefore, the present study aimed to perform a systematic review and meta-analysis of controlled clinical trials to assess the effect of L-carnitine supplementation on serum liver enzymes (ALT, AST, and GGTP) in adults.

MATERIALS AND METHOD

The present systematic review and meta-analysis is reported based on preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines and aimed to investigate the effect of L-carnitine supplementation on circulating ALT, AST, and GGTP levels in adults. The study protocol was registered and ethically approved by the research council of Shahid Sadoughi University of Medical Sciences (registration code: IR.SSU.SPH.REC.1398.016).

Search strategy

Relevant articles were identified by searching PubMed (www.pubmed.com), Scopus (http://www.scopus.com), ISI Web of Science (www.webofknowledge.com), and Google Scholar (www.scholar.google.com) from the earliest available online indexing year to June 2019. No language restriction or other filters were applied when searching the literature. The following groups of medical subject headings (MeSH) and non-MeSH keywords were used: *keywords group 1:* "carnitine", "levocarnitine", "vitamin BT", "bicarnesine", "acetylcarnitine", "hydroxyisovalerylcarnitine", "palmitoylcarnitine", "L-carnitine", "propionyl-L-carnitine", "L-carnitine L-tartrate", "L-Carnitine-L-tartrate", "L-carnitine Tartrate"; *keywords group 2:* "intervention", "trial", "randomized", "random", "randomly", "placebo", "assignment", "clinical trial", "RCT", "cross-over", "parallel", "steatosis", "steatoses", "non-alcoholic fatty liver disease", "nonalcoholic fatty liver disease", "NAFLD", "nonalcoholic fatty liver", "nonalcoholic steatohepatitis", "nonalcoholic steatohepatitides", "alanine transaminase", "glutamic-alanine transaminase", "glutamic alanine", "alanine-2-oxoglutarate aminotransferase", "alanine 2 oxoglutarate aminotransferase", "ALT", "alanine aminotransferase", "SGPT", "glutamic-pyruvic transaminase", "glutamic pyruvic transaminase", "SGOT", "glutamic-oxaloacetic transaminase", "glutamic oxaloacetic transaminase", "AST", "aspartate aminotransferases", "aspartate apoaminotransferase",

123 "aspartate transaminase", "glutamic-oxaloacetic transaminase", "glutamic oxaloacetic
124 transaminase", "L-aspartate-2-oxoglutarate aminotransferase", "L aspartate 2 oxoglutarate
125 aminotransferase", "glutamate-aspartate transaminase", "glutamate aspartate transaminase",
126 "GGTP", "gamma-glutamyl transpeptidase", "ALP", "alkaline phosphatase"; *Keywords group*
127 *3*: "mouse", "mice", "rats", "in vitro", "pig", "rabbit", "rooster", "cell", "cow". Group 1
128 keywords were combined with group 2 by "AND" operator and the "NOT" Boolean was used
129 to remove publications with keywords group 3 in their titles/abstracts. Moreover, the keywords
130 related to anthropometric indices, glycemic and inflammatory markers, blood pressure, lipid
131 profile, and oxidative stress were used to find relevant studies reporting liver enzymes as
132 secondary outcomes. The details on search strategy for PubMed, Scopus, and ISI web of
133 science are provided in the **Supplementary Table 1**.
134
135 **Eligibility criteria**
136 The population, intervention, comparison, outcome, and study types (PICOS) criteria used for
137 the current study are shown in **Table 1**. The following inclusion criteria were considered for
138 selecting the relevant investigations: 1) studies which were controlled clinical trial in design
139 (randomized or non-randomized); 2) studies which assessed the effect of L-carnitine
140 supplementation on circulating liver enzymes [e.g. ATL, AST, and other possible markers like
141 gamma-glutamyl transpeptidase (GGTP), and alkaline phosphatase (ALP)] levels; 3) studies
142 conducted in adults aged 18 years and more.
143 Trials were excluded for the following reasons: 1) they were performed in children or
144 adolescents aged younger than 18 years; 2) studies with ≤ 1 week (wk) of intervention duration;
145 3) trials in which the difference between the intervention and control group was in other
146 components in addition to L-carnitine supplementation; 4) studies in which L-carnitine was
147 injected intravenously or intramuscularly; 5) studies which did not assess outcomes of interest;

6) studies reporting duplicate data. In the case of several publications with the same data set, publications with more complete data were selected.

The preliminary screening of titles and abstracts of all identified articles, as well as further reviewing of the full-texts of the eligible papers, were independently done by two investigators (FP and NT), and any disagreement was resolved by consulting other authors (ASA, MM, and NRJ). In addition, the reference lists of relevant original and review articles were manually scanned to identify any other potentially eligible studies.

Data extraction

The data extracting process was done by 2 independent reviewers (FP and NT). This process was approved by other investigators (ASA, MM, and NRJ). The following information was recorded from eligible studies: the last name of the first author, the year of publication, the country in which the study was implemented, the design of the study, intervention duration (weeks), the mean/range of participants' age, the number of participants, the participants' health status, the dosage of L-carnitine supplement (mg/day), the intervention carried out in the control group, and the outcome measures. To obtain the data that were not mentioned in the studies, we emailed the corresponding authors of the eligible publications.

Risk of bias assessment in individual studies

Two independent investigators (FP and NT) assessed the risk of bias in the included studies using the Cochrane risk of bias tool. Six domains were considered: (i) random sequence generation (selection bias); (ii) allocation concealment (selection bias); (iii) blinding of participants and personnel (performance bias); (iv) blinding of outcome assessment (detection bias); (v) incomplete outcome data (attrition bias); (vi) selective reporting (reporting bias). The included investigations were judged to be "low risk of bias", "high risk of bias", or "unclear

risk of bias" regarding each domain. A study was considered as a low risk of bias if it received a low risk of bias for all domains, unclear risk if it was unclear regarding the risk of bias for one or more domains and high risk of bias if it was a high risk of bias for one or more domains (45).

Assessment of the overall quality of the meta-analysis

The overall quality of the met-evidence provided by the current study was assessed using the NutriGrade scoring system, which uses a scoring system (with maximum of 10 points) to judge the quality of meta-analyses of clinical trials conducted in the field of nutrition. This tool considers the following domains: risk of bias/study quality/study limitations (3 points), precision (1 point), heterogeneity (1 point), directness (1 point), funding bias (1 point), publication bias (1 point), and study design (2 point) (46). NutriGrade suggests 4 categories for the overall quality of meta-evidence, including high (≥ 8 points), moderate (6-7.99 points), low (4-5.99 points) and very low (≤ 3.99 points).

Statistical analysis

The mean change values from baseline to follow-up and their standard deviations (SDs) for intervention and control groups/periods were extracted to calculate the mean difference and its corresponding standard error (SE), which was used as the effect size for meta-analysis. If the change values were not reported, we calculated the SD for mean change by calculating correlation coefficients (r = 0.76 for ALT and r = 0.65 for AST) from studies which already reported SDs for baseline, after intervention and change values for the intervention and the control groups (36, 38, 40, 42, 47). The correlation coefficients were used to calculate SD for change values for other studies (45). The overall mean differences (MDs) and their corresponding 95% confidence intervals (CIs) were calculated by using the random effects

198 model that takes the between-study heterogeneity into account (48). The Cochrane Q test and
199 I-squared statistic (I^2 is an estimate ranging from 0-100%, with lower values indicating less
200 heterogeneity) were used to assess the heterogeneity between studies (49). The possible sources
201 of heterogeneity were explored by using subgroup analysis based on the health status of
202 participants (liver disease/without liver disease), type of control group (without
203 treatment/placebo/drug), follow-up time (≤12 weeks / >12 weeks), and dosage of L-carnitine
204 supplement (<2000 mg/d / ≥2000 mg/d). Sensitivity analysis was used to assess the robustness
205 of the meta-analyses results by sequentially removing individual included studies. The
206 presence of publication bias was assessed for each outcome through statistical asymmetry tests
207 (Egger's regression asymmetry test and Begg's adjusted rank correlation test), and also by
208 visually inspecting Begg's funnel plot. All statistical analyses were performed using STATA,
209 version 11.2 (Stata Corp, College Station, TX) and a two-sided P-values < 0.05 were
210 considered as statistically significant.

RESULTS

Study selection

The literature search retrieved 6321 publications, of which 1355 papers were duplicates, and 4920 papers were excluded after screening the titles and abstracts. After full-text assessment of 46 potentially relevant records, 27 studies were excluded because they did not report the outcomes of interest (n=14) (50-63); supplemented other components in addition to L-carnitine, and the difference between the two groups/periods was not only in L-carnitine (n=3) (64-66); included duplicate data from the other studies (n=7) (67-73); administered L-carnitine intramuscularly (n=1) (74); the intervention period was lower than 2 weeks (n=1) (75); conducted in participants aged younger than 18 years (n=1) (76). Finally, 19 controlled clinical trials which studied a total of 1206 subjects were selected to be included in the present systematic review and meta-analysis (35-44, 47, 77-84). The detailed steps of the study selection process are shown in **Figure 1**.

Study and participant characteristics

Twelve studies were carried out in Asian countries (37, 40-44, 77-79, 82-84) and seven studies were done in European countries (35, 36, 38, 39, 47, 80, 81), published between 1996 and 2016. All trials used a parallel design, except one study which used cross over design (80), and the intervention period in these studies ranged between 2 and 48 wks. L-carnitine was orally administered and the intervention dose ranged between 500 to 4000 mg/day. For the control groups, ten trials used placebo controls (35, 36, 39, 44, 79-84), six trials did not prescribe any treatment (37, 40-43, 77), and three trials used drugs such as interferon-α, ribavirin, and entecavir, in which participants in the intervention group also received these drugs in addition to L-carnitine (38, 47, 78). The majority of trials included either gender, with the age ranging

from 18 to 85 years. The sample size of included studies ranged from 30 to 131 participants. Nine trials were conducted among participants who had liver diseases (36-38, 43, 47, 77-79, 81). Two trials were done in hemodialysis patients (40, 41), one study included participants with hypothyroidism (44), cystic acne patients (35) and thyroid patients (80). One study was conducted in obese women (42), three trials included healthy participants (39, 82, 83) and one study included patients with suspected acute myocardial infraction (84). The characteristics of the included studies are detailed in **Table 2**.

Risk of bias assessment

A summary of the risk of bias assessment of the included studies is presented in **Table 3**. Although the description for the random generation was well-addressed in six studies (36, 38, 41, 44, 47, 78, 79, 82), others did not explain random sequence generation method, and one of the studies was not randomized (37). Two trials included information about allocation concealment (82, 85). Four studies were considered to be a low risk of bias regarding blinding of participants and personnel (36, 39, 79-85). In the majority of included trials, the blinding of outcome assessment was unclear. Incomplete outcome data were addressed in thirteen studies (36, 38-41, 44, 47, 78, 79, 81-84). All trials were categorized as low risk of bias for selective outcome reporting. Considering the six domains of the Cochrane collaborations' risk of bias assessment tool, fifteen trials were judged to have a moderate or unclear risk, and four trials had a high risk of bias.

The effect of L-carnitine on serum alanine aminotransferase (ALT) concentrations

Seventeen trials, including 1091 participants, provided data on the effect of L-carnitine supplementation on serum ALT levels (35-43, 47, 77-81, 83, 85). The pooled effect size indicated that consuming L-carnitine significantly reduced ALT concentrations (MD = -10.97

IU/L, 95% CI: -16.46, -5.48, P < 0.001), with high between-study heterogeneity (Q statistic = 606.33, Cochrane Q test, P < 0.001; I^2 = 97.4). Although, heterogeneity was not reduced by several subgroup analyses, the results showed that serum ALT levels were reduced to a greater magnitude in patients with liver diseases (MD = -20.25 IU/L, 95% CI: -31.22, -9.28, P < 0.001; **Figure 2A**), compared with subjects without liver diseases (MD = -2.84 IU/L, 95% CI: -5.33, -0.34, P = 0.026). In another subgroup analysis, based on the type of control group, in studies which administered placebo or drug for the control group compared with studies that did not use any treatment for controls, a significant reduction in the levels of ALT was observed. There was also a significant reduction in serum ALT concentrations following L-carnitine supplementation in studies which used high doses of L-carnitine (≥ 2000 mg/day) for supplementation (MD = -14.08 IU/L, 95% CI: -22.72, -5.44, P = 0.001; **Figure 3A**). However, significant changes were not observed in lower intervention doses. Moreover, the reducing effect of L-carnitine on serum ALT levels was seen in both subgroups of duration; however, the effect was lower for studies with a duration of shorter than 12 weeks. **Table 4** shows the meta-analysis results for subgroup as well as overall analyses.

The effect of L-carnitine on serum aspartate aminotransferase (AST) concentrations

The results of the overall analysis of eighteen studies with 1087 participants (35-43, 47, 77, 79-85) indicated that circulating AST levels following L-carnitine supplementation was significantly decreased compared to control groups (MD = -9.03 IU/L, 95% CI: -12.73, -5.33, P < 0.001). The heterogeneity between studies was significant (Q statistic =313.44, Cochran's Q test, P < 0.001; I^2 = 94.6), and was not explained by several subgroup analyses. The results of the subgroup analysis based on health status of participants indicated a greater reduction in serum AST levels among patients with liver diseases as compared to patients without liver disease (MD = -17.39, 95% CI: -24.10, -10.76, P < 0.001 vs. MD = -4.32, 95% CI: -7.45, -

1.18, P = 0.007; **Figure 2B**). Pooled analysis of studies, in which control subjects received placebo or drug, showed a significant reduction, while there was no considerable difference in serum AST levels in studies with non-treated controls. We also observed that L-carnitine supplementation in studies with intervention doses of ≥ 2000 mg/day significantly reduced circulating AST levels compared with control groups (MD = -13.53, 95% CI: -19.43, -7.63, P < 0.001; **Figure 3B**), however, there was no significant change when the analysis was done for studies with intervention doses of less than 2000 mg/day. Moreover, the reducing effect of L-carnitine on serum AST levels was seen in both subgroups of duration; however, the effect was lower for studies with a duration of shorter than 12 weeks. **Table 4** details the overall, as well as subgroup analyses, results.

The effect of L-carnitine on other liver enzymes

The pooled estimate of six trials (35-37, 43, 80, 83) evaluating the effect of L-carnitine supplementation on serum GGTP levels showed a significant reduction (MD = -7.88 IU/L, 95% CI: -12.11, -3.64, P < 0.001), with no significant between-study heterogeneity (Q statistic = 7.39, Cochran's Q test, P = 0.193; I^2 = 32.4%).

Sensitivity analysis and publication bias

The sensitivity analysis revealed that the significant effect of L-carnitine supplementation on circulating ALT and AST levels did not change by removing any of the included trials. The summary effect of the L-carnitine on GGTP levels changed to a non-significant reduction after removing the Lim et al. study (37) (MD = -10.08 IU/L, 95% CI: -20.55, 0.38) and Georgala et al. study (35) (MD = -9.84 IU/L, 95% CI: -21.51, 1.83). We also performed a sensitivity analysis to assess whether results varied by the quality of studies. The results showed that, by excluding the trials that had high risk of bias in overall assessment (37, 38, 41, 78), the

311 significant reducing effect of L-carnitine supplementation on circulating ALT and AST levels
312 was unaltered.
313 No evidence of publication bias was found regarding the effect of L-carnitine consumption on
314 ALT (Begg's test, P = 0.077; Egger's test, P = 0.097) and GGTP (Begg's test, P =1.00; Egger's
315 test, P = 0.918) levels. However, visual examination of funnel plot, as well as Begg's and
316 Egger's asymmetry tests (Begg's test, P =0.034; Egger's test, P = 0.009), suggested evidence
317 of publication bias for the meta-analysis of serum AST levels. However, using the trim and fill
318 analysis, which conservatively imputes estimates from hypothetical negative unpublished
319 studies, we found the results remained unchanged.
320
321 **Quality of meta-evidence**
322 The total scores of quality of meta-evidence, which was assessed using the NutriGrade scoring
323 system, were 6.6 for ALT and AST (indicating moderate confidence in the effect estimate,
324 which shows future well designed clinical trials are still needed to confirm our results), and 4.4
325 for GGTP (indicating low confidence in the effect estimate, which shows further research will
326 provide important evidence on the confidence and likely change the effect estimate).

DISCUSSION

In the present systematic review and meta-analysis, we assessed the efficacy of L-carnitine supplementation in reducing serum liver enzyme levels; by reviewing the available published controlled intervention trials, for the first time. The synthesis of the data confirmed the beneficial effect of L-carnitine intake on decreasing ALT, AST, and GGTP levels. The subgroup analysis showed that L-carnitine might be more effective in reducing liver enzymes when higher doses (≥ 2000 mg/day) are supplemented, when the treatment duration is more than 12 weeks and also when the supplementation is done in patients with liver diseases.

The absorption of oral L-carnitine across the intestinal cells occurs through both active and passive means of transport. These pathways assure the high concentration of L-carnitine in tissues that are dependent on fatty acids oxidation as a fuel source (86, 87). Oral supplementation of L-carnitine (1-6 gr) has been reported to have a biological availability between 5-18% (86), and this limited bioavailability might be associated with metabolization of L-carnitine by gut microbiota prior to absorption (88, 89). This point may be a logical explanation for the efficacy of higher doses of L-carnitine in reducing ALT and AST levels (30). It has been stated that supplementation with L-carnitine is regarded as safe for doses up to 15 g/day in healthy men (42), although doses of 100-400 mg/kg/day is recommended in carnitine deficiency, and, importantly, the L-carnitine dose should be compatible with each patient by measurement of plasma L-carnitine levels. A few side effects, like diarrhea, intestinal problems and the production of trimethylamine, resulting in a fishy odor, have also been observed following high doses of L-carnitine supplementation, which can be effectively treated by reducing the dosage (90).

In the current meta-analysis, we observed a significant reduction in circulating ALT and AST levels following supplementation with L-carnitine in patients with and without liver diseases, however, this reduction was higher in patients with liver diseases compared with other

participants. Indeed, it seems that L-carnitine supplementation elicits a greater beneficial effect for patients who have high levels of liver enzymes at baseline. Since the liver is a major organ responsible for detoxification and metabolization of various compounds that produce reactive oxygen species (ROS), liver diseases might lead to increased ROS production (91, 92). Consequently, oxidative stress induces impairments in mitochondrial β-oxidation (93, 94). The disruption of β-oxidation is a major contributor in the pathogenesis of nonalcoholic fatty liver disease, which causes the accumulation of fatty acids within the hepatocytes and the progression of the disease (95-97). Therefore, the essential role of L-carnitine in the transfer of the long-chain fatty acids inside mitochondria for β-oxidation might be a reason for reducing ALT and AST levels, especially in patients with liver disease (31, 98, 99). Furthermore, it has been proposed that L-carnitine, due to antioxidant and antiradical properties, might be useful in preventing oxidative stress and the activity of enzymes involved in defense reactions against oxidative damage (100). On the other hand, carnitine deficiency is more likely to occur in liver diseases (47, 101), which impairs the mitochondrial β-oxidation of fatty acids, causing acute metabolic decompensation with elevated transaminases, hepatic encephalopathy, hypoketotic hypoglycemia, and cardiomyopathy (102). Accordingly, the correction of carnitine deficiency by oral supplementation of L-carnitine might be beneficial in these patients (101).

There are a number of limitations in the present meta-analysis, although some of them are associated with inherent shortcomings of clinical trials such as heterogeneous methodological approaches regarding the characteristics of participants (for instance, changes in carnitine metabolism in uremia and its depletion is expected in hemodialysis patients), L-carnitine dosage (500-4000 mg/d), and type of control group (placebo, drug or without treatment). Moreover, the duration of L-carnitine supplementation varied from study-to-study, therefore further studies are needed to examine the time-dependent effect of L-carnitine supplementation in reducing ALT and AST levels. Also, a number of the included studies did not explain the

method used to assess the adherence to the treatment, for instance, pill counts or measurement of serum carnitine (37, 39, 42, 43, 77, 78). On the other hand, the bioavailability of L-carnitine was not assessed in the included studies, so the amount of available L-carnitine in the blood after ingestion is not clearly specified. It is also important to note that these findings should not be generalized to patients with primary or secondary carnitine deficiency (caused by genetic alterations in renal handling or muscle transport of L-carnitine and impaired renal tubular resorption from drug toxicity or hemodialysis, respectively). In contrast to these limitations, there are several strengths in our study. We conducted a comprehensive and systematic search to identify all published studies on this topic. We also performed several subgroup analyses to evaluate the potentially different effects of L-carnitine supplementation caused by the intervention dose and duration, the type of control group, and the health status of the participants. Moreover, the findings of the present meta-analysis were not sensitive to the results of any one of the included studies, which highloghts the robustness of the findings.

The present systematic review and meta-analysis provides evidence for the beneficial effects of L-carnitine supplementation in reducing serum liver enzyme levels. Our findings also showed that L-carnitine can be more effective among patients with liver diseases and with intervention doses of more than 2000 mg/day. However, since the majority of the included studies were judged to be have an “unclear” risk of bias, the authors suggest that further high-quality trials, with an adequate duration and sample size, are conducted to reliably confirm the efficacy and safety of L-carnitine supplementation in improving liver enzymes.

Conflict of Interest

There is no conflict of interest to report for this study.

Contributions of authors

The responsibilities of authors were as follows: ASA, MM, and NRJ developed the search strategy; FP, NT and MM conducted the electronic searches and study selection; FP, NRJ, and MM conducted data extraction and tabulated data; ASA, MM, and NRJ conducted the data analysis and interpretation of results; FP, NRJ, and NT wrote the first draft of the manuscript; ASA and CC revised the manuscript and all authors read and approved its final version.

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Table 1- The Population, Intervention, Comparison, Outcome, Study types (PICOS) criteria

Criteria	Description
Population	Adults aged >18 year
Intervention	L-carnitine supplement
Comparison	Placebo, without treatment or other drugs/supplements
Outcome	Enzymes mainly produced by liver [.alanine aminotransferase (ATL), aspartate aminotransferase (AST), and other possible markers like gamma-glutamyl transpeptidase (GGTP), alkaline phosphatase (ALP)]
Study types	Controlled clinical trials

Table 2. Characteristics of controlled clinical trials that were included in the systematic review

Study, Year (ref)	Country	Number, Sex (F/M)*	Age (year)	Study design	Duration (weeks)	Intervention group	Control group	Reported outcomes	Notes about participants
An et al., 2016 (85)	Korea	53 F/M	20-80 Int: 49 Con: 50.9	Parallel	12	Three tablet twice per day, 330 mg L-carnitine in each tablet	Placebo	ALT* AST*	Patients with hypothyroidism on levothyroxine treatment
Alavinejad et al., 2016 (79)	Iran	54 16F/38M	Int: 60 Con: 59	Parallel	12	750 mg L-carnitine three times day	Placebo	ALT AST	Type 2 diabetic patients with NAFLD*
Mosah et al., 2015 (42)	Iraq	60 F	20-40 Int: 33.11 Con: 32.72	Parallel	12	1000 mg/d L-carnitine	Without treatment	ALT AST	Obese women with a BMI* $\geq$ 30 kg/m^2
Hassan et al., 2015 (43)	Japan	50 12F/38M	Int: 24 Con: 26	Parallel	12	600 mg/day L-carnitine	Without treatment	ALT AST GGTP*	Patients in intermediate stage hepatocellular carcinoma
Higuchi et al., 2014 (41)	Tokyo	131 F/M	20-85 Int: 67 Con: 68	Parallel	48	20 mg/kg/day L-carnitine	Without treatment	ALT AST	Hemodialysis patient
Somi et al., 2014 (77)	Iran	80 66F/14M	25-62 Int: 40.3 Con: 41.1	Parallel	24	500 mg/d L-carnitine	Without treatment	ALT AST	Patient with NAFLD
Fukami et al., 2013 (40)	Japan	70 26F/44M	Int: 68 Con: 67	Parallel	24	900 mg/d L-carnitine	Without treatment	ALT AST	Hemodialysis patient
Jun et al., 2013 (78)	Korea	119 42F/77M	Int: 43 Con: 44.9	Parallel	48	2472 mg/d L-carnitine + 0.5 mg entecavir	0.5 mg entecavir	ALT	Hepatitis B patients

Odo et al., 2013(83)	Japan	21 M	20-60 Int: 44.4 Con: 40.2	Parallel	4	500 mg/d L-carnitine	Placebo	ALT AST GGTP	Healthy volunteers (overweight)
Mohtadinia et al., 2013 (82)	Iran	14 M	Int: 20.7 Con: 21.2	Parallel	3	2000 mg/d L-carnitine	Placebo (2000 mg/d maltodextrin)	AST	Healthy male football players
Malagurnera et al., 2011 (38)	Italy	69 27F/42M	Int: 35 Con: 34	Parallel	48	2000 mg L-carnitine twice a day + 1.5 µg/kg/wk peg interferon-α 2b + ribavirin	1.5 µg/kg/wk peg interferon-α 2b + ribavirin	ALT AST	Patients with chronic hepatitis C virus
Malaguarnera et al., 2010 (36)	Italy	74 34F/40M	28-60 Int: 47.9 Con: 47.8	Parallel	24	2000 mg/d L-carnitine + 1600-calorie diet	2000 mg/d Placebo + 1600-calorie diet	ALT AST GGTP	Patient with nonalcoholic steatohepatitis
Lim et al., 2010 (37)	Korea	45 F/M	Int: 29 Con: 16	Parallel	12	600 mg/d L-carnitine	Without treatment	ALT AST GGTP	Patient with non-alcoholic fatty liver disease
Delas et al., 2008 (39)	Croatia	30 18F/12M	18-32 Int: 23.1 Con: 21.3	Parallel	2	2000 mg/d L-carnitine	2000 mg/d Placebo	ALT AST	Healthy volunteers
Malaguarnera et al., 2008 (81)	Italy	115 47F/68M	Int: 48 Con: 45	Parallel	12	2000 mg Acetyl-L-carnitine twice daily	Placebo	ALT AST	Cirrhotic patients with minimal hepatic encephalopathy
Malaguarnera et al., 2002 (47)	Italy	70 27F/43M	NR Int: 56.8 Con: 57.7	Parallel	24	2000 mg/d L-carnitine + 3 million IU Interferon-α three times a week	3 million IU Interferon-α three times a week	ALT AST	Patient with chronic hepatitis C treated with Interferon-α

Benvenga et al., 2001(80)	Italy	10 F	Int: 43.4 Con: 43.4	Cross-over	8	4000 mg/d L-carnitine + l-thyroxine	Placebo + l-thyroxine	ALT AST GGTP	Thyroid patients
Georgala et al., 1999 (35)	Athene	40 F/M	NR	Parallel	6	100 mg/kg/day L-carnitine	100 mg/kg/day Placebo	ALT AST GGTP	Patient with cystic acne on isotretinoin therapy
Singh et al, 1996 (84)	India	101 10F/91M	Int: 49.2 Con: 50.5	Parallel	4	2000 mg/d L-carnitine	Placebo	AST	Patients with suspected acute myocardial infarction

*ALT, alanin aminotransferase; AST, aspartat aminotransferase; GGTP, gamma-glutamyl transpeptidase; Con, control; F, female; Int, intervention M, male; NR, not reported; NAFLD, non-alcoholic fatty liver disease

Table 3. Risk of bias assessment according to the Cochrane collaboration's risk of bias assessment tool

Study, Year (ref)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Summary of overall assessment
An et al., 2016 (85)	Low	Low	Low	Unclear	Low	Low	Unclear
Alavinejad et al., 2016 (79)	Low	Unclear	Low	Unclear	Low	Low	Unclear
Mosah et al., 2015 (42)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Hassan et al., 2015 (43)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Higuchi et al., 2014 (41)	Low	High	High	Unclear	Low	Low	High
Somi et al., 2014 (77)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Fukami et al., 2013 (40)	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Jun et al., 2013 (78)	Low	High	High	Unclear	Low	Low	High
Odo et al., 2013 (83)	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Mohtadinia et al., 2013 (82)	Low	Low	Low	Unclear	Low	Low	Unclear
Malagurnera et al., 2011 (38)	Low	High	High	Unclear	Low	Low	High
Malaguarnera et al., 2010 (36)	Low	Unclear	Low	Low	Low	Low	Unclear
Lim et al., 2010 (37)	High	High	High	Unclear	Unclear	Low	High
Delas et al., 2008 (39)	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Malaguarnera et al, 2008 (81)	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Malaguarnera et al., 2002 (47)	Low	Unclear	Unclear	Unclear	Low	Low	Unclear
Benvenga et al., 2001 (80)	Unclear	Unclear	Low	Unclear	Unclear	Low	Unclear
Georgala et al., 1999 (35)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Singh et al., 1996 (84)	Unclear	Unclear	Low	Unclear	Low	Low	Unclear

Table 4- The effect of L-carnitine supplementation on serum ALT and AST levels based on several subgroups as well as all studies, using a random-effects model.

			Meta-analysis		Heterogeneity			
	Trials, n	**Subjects, n**	**Weighted mean difference (95% CI)**	***P* effect**	***Q* statistic**	***P* within group**	**I^2 (%)**	***P* between group**
ALT (IU/L)								
Health status								
Liver disease	9	676	-20.25 (-31.22, -9.28)	<0.001	143.59	<0.001	94.4	<0.001
Without liver disease	8	415	-2.84 (-5.33, -0.34)	0.026	50.71	<0.001	86.2	
Control type								
Without treatment	6	436	-8.85 (-17.74, 0.04)	0.051	260.51	<0.001	98.1	<0.001
Placebo	8	397	-10.19 (-18.97, -1.42)	0.023	296.38	<0.001	97.6	
Drug	3	258	-23.51 (-37.35, -9.68)	0.001	2.35	0.309	14.9	
Dosage of L-carnitine								
< 2000 mg/d	7	457	-7.52 (-15.54, 0.49)	0.066	261.58	<0.001	97.7	<0.001
≥ 2000 mg/d	10	634	-14.08 (-22.72, -5.44)	0.001	297.39	<0.001	97	
Duration								
≤ 12 weeks	10	478	-9.59 (-17.54, -1.64)	0.018	523.25	<0.001	98.3	0.099
> 12 weeks	7	613	-12.77 (-20.63, -4.90)	0.001	80.37	<0.001	92.5	
Overall	17	1091	-10.97 (-16.64, -5.48)	<0.001	606.33	<0.001	97.4	-
AST (IU/L)								
Health status								
Liver disease	8	557	-17.39 (-24.10, -10.67)	<0.001	36.57	<0.001	80.9	<0.001
Without liver disease	10	530	-4.32 (-7.45, -1.18)	0.007	119.94	<0.001	92.5	
Control type								
Without treatment	6	436	-3.91 (-9.19, 1.36)	0.146	79.39	<0.001	93.7	<0.001
Placebo	10	512	-10.77 (-16.37, -5.18)	<0.001	204.09	<0.001	95.6	
Drug	2	139	-29.10 (-43.66, -14.53)	<0.001	0.49	0.482	0	
Dosage of L-carnitine								
< 2000 mg/d	7	457	-3.14 (-7.72, 1.43)	0.179	81.27	<0.001	92.6	<0.001
≥ 2000 mg/d	11	630	-13.53 (-19.43, -7.63)	<0.001	204.42	<0.001	95.1	
Duration								
≤ 12 weeks	12	593	-8.62 (-13.06, -4.18)	<0.001	253.37	<0.001	95.7	0.604
>12 weeks	6	494	-10.82 (-19.16, -2.47)	0.011	59.81	<0.001	91.6	
Overall	18	1087	-9.03 (-12.73, -5.33)	<0.001	313.44	<0.001	94.6	-
GGTP (IU/L)								
Overall	6	240	-7.88 (-12.11, -3.64)	<0.001	7.39	0.193	32.4	-

Figure Legends

Figure 1- The detailed steps of the study selection process.

Figure 2- Forest plots of controlled trials examining the pooled effects of L-carnitine, based on the health status of participants (liver disease/without liver disease) on serum levels of alanine aminotransferase (ALT) (A), and aspartate aminotransferase (AST) (B).

Figure 3- Forest plots of controlled trials examining the pooled effects of L-carnitine, as well as based on the intervention dose of supplementation (< 2000 mg/d/≥ 2000 mg/d) on serum levels of on serum levels of alanine aminotransferase (ALT) (A), and aspartate aminotransferase (AST) (B).