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REVIEW ARTICLE

Effects of carnitine supplementation on liver aminotransferase enzymes: A systematic review and meta-analysis of randomized controlled clinical trials

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Abstract

Background and Aims This meta-analysis of the randomized controlled trials was performed to assess effects of carnitine supplementation on serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.

Methods A comprehensive literature search of PubMed, Cochrane's library, Web of Science, Scopus, and Embase was performed up to May 2018. From a total of 2012 articles identified initially, only 17 articles were included in the final meta-analysis to evaluate the effects of carnitine supplementation on serum levels of ALT and AST enzymes.

Results Random effects model meta-analysis showed that carnitine supplementation led to reduction in serum ALT (weighted mean difference [WMD] − 10.25 IU/L; 95% CI = − 15.73, − 4.77; $p < 0.001$) and AST levels (WMD − 7.85 IU/L; 95% CI = − 11.85, − 3.86; $p < 0.001$). The results of subgroup analysis showed that carnitine could reduce serum AST levels at dosages equal to 2000 mg/day ($p = 0.014$) or more than 2000 mg/day ($p < 0.001$). However, carnitine supplementation at dosages of ≤ 1000 mg/day ($p = 0.035$) or equal to 2000 mg/day ($p = 0.013$) resulted in significant reduction in ALT level, while doses more than 2000 mg/day did not change ALT significantly. Carnitine exerts its reducing effect on serum ALT and AST levels only when these aminotransferases are raised or when the duration of supplementation lasts at least 3 months.

Conclusion Results of the current meta-analysis showed that carnitine supplementation can decrease serum AST and ALT levels significantly, especially when supplementation lasts 3 months or more in patients with elevated serum aminotransferase levels.

Keywords Alanine aminotransferase · Aspartate aminotransferase · Carnitine · Liver enzymes · Meta-analysis

Introduction

L-carnitine is a vitamin-like compound which can be synthesized endogenously in the liver and kidneys from the essential amino acids lysine and methionine [1]. It can also be found in abundant levels in animal sources especially red meat, poultry, fish, and dairy products [2]. The main function of carnitine in the human body is transportation of long-chain fatty acids from the cytoplasm into the mitochondria mediated by carnitine palmitoyltransferase enzymes for beta-oxidation. So, it is essential for normal energy production and regulation of ketogenesis [3]. It is also involved in oxidative pathways by protecting antioxidant enzymes [4], cell membrane stabilization [3], and repair of single-strand breaks in damaged DNA [5]. Several meta-analysis confirmed that carnitine supplementation could improve overall health outcomes of patients with chronic kidney disease [6], depression [7], insulin

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resistance [8], and chronic heart failure [9]. Studies showed that carnitine deficiency could be associated with liver cirrhosis [10] and its supplementation can improve liver enzyme status in patients with chronic hepatitis B and C [11, 12].

The liver aminotransferases including, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are among commonly used laboratory tests, which do not require a fasting state and are inexpensive and well standardized. For these reasons, these are used extensively for diagnosis of liver diseases [13, 14]. Effects of carnitine supplementation on serum levels of ALT and AST had been investigated in several clinical trials in patients with compromised liver function. Alavinejad et al. in one study on type 2 diabetic patients with non-alcoholic fatty liver disease (NAFLD) showed that 3 months supplementation with 750 mg/day carnitine could decrease serum levels of ALT and AST in these patients significantly[15]. Another study on patients with minimal hepatic encephalopathy showed that supplementation with 2 g/day carnitine for 2 and 3 months could decrease serum AST level significantly though it did not show any significant reducing effect on serum ALT level [16]. However, Romano et al. in a study on patients with moderate stages of hepatic encephalopathy showed that 3 months supplementation with acetyl-L-carnitine could only decrease serum ALT level significantly [17]. Hassan et al. in a clinical trial concluded that oral administration of carnitine in dosage of 600 mg/day for 6 and 14 weeks did not significantly change serum levels of ALT and AST patients with hepatocellular carcinoma (HCC) undergoing transarterial chemoembolization (TACE) [18]. Because of these conflicting results, the current meta-analysis was conducted to pool the effects of carnitine supplementation on serum levels of ALT and AST enzymes in clinical trials.

Methods

Search strategy and study selection

A comprehensive literature search of 5 databases including PubMed, Cochrane's library, Web of Science, Scopus, and Embase was conducted independently by two authors (EE, OA) with the use of the following keywords: "aspartate aminotransferase or alanine aminotransferase or AST or ALT or SGOT or SGPT or NAFLD or liver enzyme or non-alcoholic fatty liver disease" in combination with "L-Acetyl-carnitine or

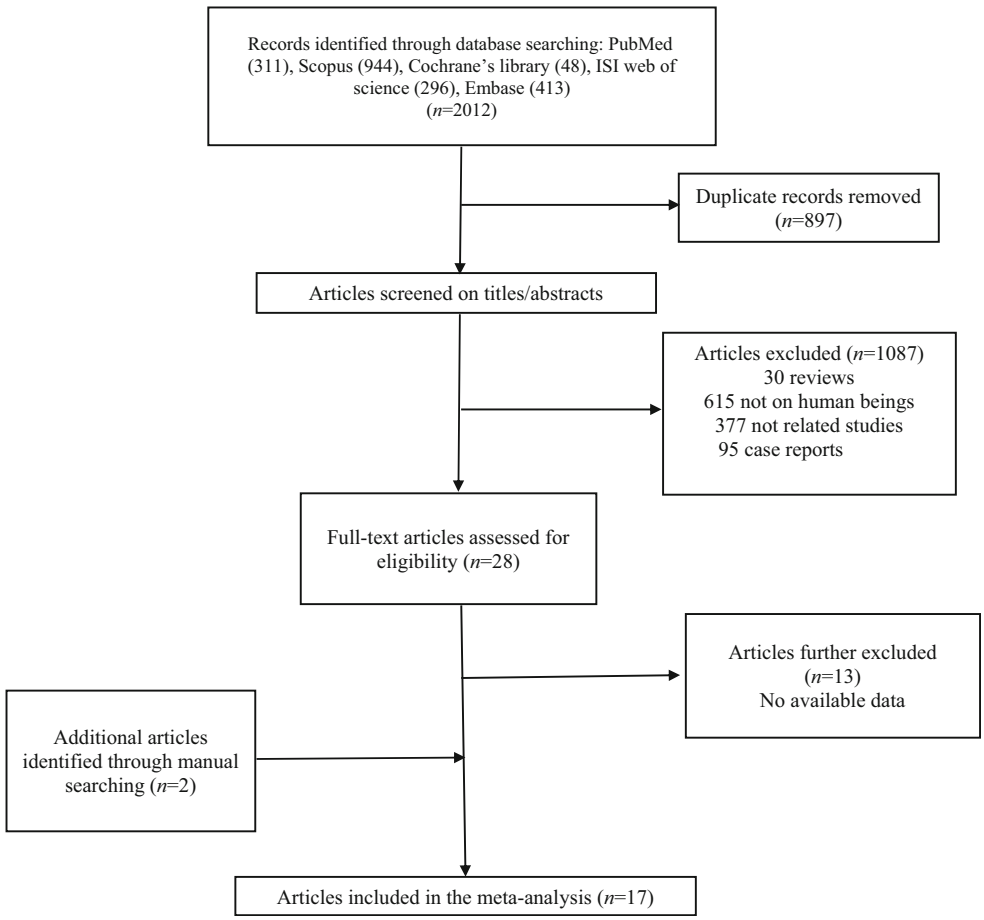

Fig. 1 Flowchart of study selection for inclusion of the trials in the systematic review

Table 1 Characteristics of the studies included in the meta-analyzes

Author	Year	Country	Study design	Participants	Sex	Mean age (intervention/control)	Mean BMI (intervention/control)	Trial duration (week)	Daily dose of carnitine (mg)	Sample size in the intervention group	Sample size in the control group
Singh et al. [22]	1996	India	R/DB/PC	The patients with suspected acute myocardial infarction	M/F	49.2/50.5	NR/NR	4	1980	51	50
Malaguarnera et al. [24]	2011	Italy	R/DB/PC	Patients with severe hepatic encephalopathy	M/F	37–64/35–65	NR/NR	12.8	4000	30	30
Malaguarnera et al. [26]	2011	Italy	R/DB/PC	Patients with minimal hepatic encephalopathy	M/F	37–65/34–67	NR/NR	12.8	4000	33	34
Somi et al. [23]	2014	Iran	R/C	Non-alcoholic fatty liver disease patients	M/F	40.7/40.7	29.4/28.6	24	500	40	40
Delas et al. [20]	2008	Croatia	R/DB/PC	Healthy volunteers with declared sedentary activities	M/F	23.1/21.3	22.7/23.8	2	2000	18	12
Alavinejad et al. [15]	2016	Iran	R/DB/PC	Diabetic patients with non-alcoholic fatty liver disease	M/F	60/59	28.6/29.5	12.8	2250	30	30
Malaguarnera et al. [28]	2010	Italy	R/DB/PC	Patients with non-alcoholic steatohepatitis	M/F	47.9/47.8	26.6/26.5	24	2000	36	38
Mosah et al. [29]	2015	Iraq	R/C	Obese women	F	33.11/32.72	34.5/34.8	12	1000	18	18
Malaguarnera et al. [25]	2002	Italy	R/C	Patients with chronic hepatitis C treated with interferon-α	M/F	56.8/57.7	26/26	25.7	2000	35	35
An et al. [32]	2016	Korea	R/DB/PC	Hypothyroidism	M/F	49/50.9	24.7/22.7	12	990	30	30
Georgala et al. [21]	1999	Croatia	R/PC	Cystic acne	NR	20.8/20.8	NR/NR	6.4	100 mg/kg	20	20
Romano et al. (2 arms) [17]	2008	Italy	R/C	Chronic hepatitis C	M/F	50.1/50.4	25.8/25.7	25.7/51.4	2000	35	35
Fukami et al. [30]	2013	Japan	R/C	Patients with hemodialysis	M/F	68/67	22.3/21.5	25.7	900	35	35
Hassan et al. (3 arms) [18]	2015	Japan	R/C	Hepatocellular carcinoma	M/F	71.6/72.3	NR/NR	1/4/12	600	8	14
Lim et al. [31]	2010	Korea	R/C	Patients with non-alcoholic fatty liver disease	M/F	49.6/42.2	NR/NR	12.8	600	24	26
Malaguarnera et al. (3 arms) [16]	2008	Italy	R/DB/PC	Cirrhotic patients with minimal hepatic encephalopathy	M/F	48/45	24.8/25.1	12.8/8.5/4.2	4000	60	55
Malaguarnera et al. (2 arms) [11]	2011	Italy	R/DB/PC	Patients with mild hepato-encephalopathy (HE1)/patients with moderate hepato-encephalopathy (HE2)	M/F	40–66/41–67	NR/NR	12.8	4000	31/30	30/30

DB double-blinded, *PC* placebo-controlled, *R* randomized, *NR* not reported, *BMI* body mass index

Bicarnesine or vitamin BT or Acetyl-l-carnitine or levocarnitine or carnitine or L-Carnitine." The search was done from inception to May 2018 without any language restriction. The reference list of eligible articles was also manually searched for completing the search process.

Inclusion and exclusion criteria

Studies were included if these had the following inclusion criteria: (1) controlled clinical trials, (2) trials with at least 1 week of duration, (3) carnitine given as intervention, (4) existence of a placebo or control group in studies, and (5) reported mean or median values of ALT or AST concentrations at baseline and at the end of supplementation in the control and intervention groups with SD, SEM, or 95% CI. Exclusion criteria were (1) studies with carnitine supplementation in combination with other nutrients, (2) studies with insufficient data at baseline and final level of ALT or AST in the control and treatment groups, and (3) observational studies, animal studies, reviews, and letter to editors.

Data extraction and quality assessment

In the initial screening, duplicate references were removed and then titles and abstracts of the remaining articles were screened for potentially relevant studies. Following this step, the full texts of the selected articles were retrieved according to the inclusion criteria, and needed data were extracted independently by two authors (EE and OA). Any disagreement in article inclusion and data extraction was solved by discussion and by the help of a third author (EY). The following data were extracted independently by the above-mentioned authors using a predefined excel form: first author name, publication year, study location, study population, study design, sample size in treatment and control groups, mean age and body mass index (BMI) of the patients, type and dose of L-carnitine supplementation, study duration, and mean ± standard deviation (SD) of liver aminotransferases in treatment and control groups. Study quality was assessed by Cochrane collaboration modified tool. This scale assesses risk of bias in the trials according to random sequence generation and allocation concealment, blinding of the participants, personnel and outcome assessment, incomplete outcome data, selective reporting, and

Table 2 Risk of bias assessment of studies included in the meta-analysis

Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data (attrition bias)	Reporting bias	Other sources of bias
Singh et al. [22]	L	U	U	U	L	U	U
Malaguarnera et al. [24]	L	U	U	U	L	U	L
Malaguarnera et al. [26]	L	L	U	U	L	U	L
Somi et al. [23]	U	U	U	U	U	U	U
Delas et al. [20]	L	U	U	U	U	U	U
Alavinejad et al. [15]	U	U	U	U	U	U	U
Malaguarnera et al. [28]	L	L	U	U	L	U	L
Mosah et al. [29]	H	H	L	H	U	U	U
Malaguarnera et al. [25]	L	L	U	U	U	U	L
An et al. [32]	L	U	L	U	U	U	L
Georgala et al. [21]	H	H	H	H	U	U	U
Romano et al. [17]	L	L	U	U	U	U	U
Fukami et al. [30]	L	U	U	U	L	U	L
Hassan et al. [18]	L	U	U	U	U	U	U
Lim et al. [31]	H	H	H	H	U	U	U
Malaguarnera et al. [16]	L	U	U	U	L	U	U
Malaguarnera et al. [11]	L	L	L	U	U	U	L

H high risk of bias, *L* low risk of bias, *U* unclear risk of bias

other bias [19]. All ALT and AST values are recorded as IU/L.

Data synthesis and statistical analysis

All statistical analyzes were performed using STATA software version 12 (Stata Corp. College Station, TX, USA). For estimation of the pooled effect size of L-carnitine supplementation on ALT and AST levels, mean changes of these variables and their SD in supplementation and placebo groups were used in a random effects model analysis. Reported standard errors of the mean (SEM) in some studies were converted to the standard deviation by use of the following formula: SD = SEM × $\sqrt{n}$ (n is the number of participants in each group). Calculation of possible heterogeneity between studies was performed using Cochran's Q test at $p < 0.05$ level of significance and the percent of heterogeneity among studies calculated by the I-square (I^2) test. To find possible sources of heterogeneity, subgroup analysis was conducted according to L-carnitine dosage, duration of intervention, and baseline levels of ALT and AST. The Begg test and Egger's regression asymmetry test were used for evaluation of publication bias. A funnel plot was also depicted for visual assessment of publication bias. P-values below 0.05 were considered significant in all analyzes.

Results

Search results and study selection

Of the 2012 articles identified in the literature search of ISI Web of Sciences, PubMed, Cochrane library, Scopus, and Embase, 897 were removed because they were duplicate findings and 1115 articles remained for the title and abstract screening. At the second step of the screening, 1087 articles were excluded because they did not have the predefined inclusion criteria and 28 remained for eligibility assessment. Subsequent to full text retrieval, quality assessment and

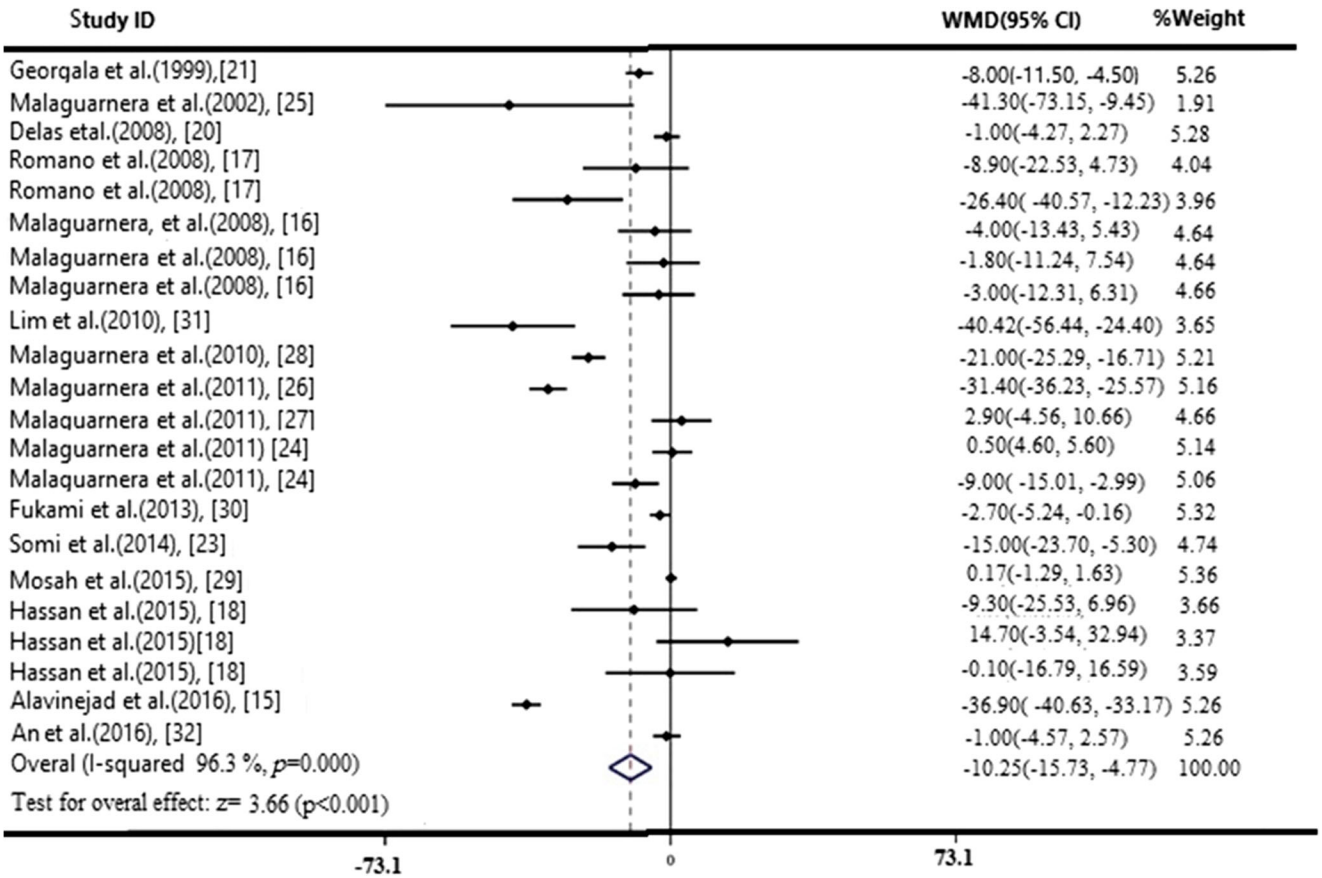

Fig. 2 Forest plot of the random effect model meta-analysis of carnitine supplementation on serum alanine aminotransferase level (IU/L). *WMD* weighted mean difference

addition of 2 articles found in manual search of included studies, 17 articles with 22 and 23 effect sizes were finally deemed suitable for pooling the effects of carnitine supplementation on serum levels of ALT and AST enzymes, respectively. The flow diagram of the study selection process is shown in Fig. 1.

Characteristics of included studies

Studies included in this meta-analysis consisted of 17 randomized clinical trials performed between 1996 and 2016 in different countries including Croatia [20], Greece [21], India [22], Iran [15, 23], Italy [16, 17, 24–28], Iraq [29], Japan [18, 30], and Korea [31, 32]. The number of participants in the intervention and control groups was 737 and 728, respectively with the age range of 20–70 years. Intervention durations varied between 1 and 51.4 weeks with the average of 14.46 weeks, and the dosages of carnitine supplements in the included trials were between 500 and 4000 mg/day. Characteristics of the included studies and their quality assessment are illustrated in Tables 1 and 2, respectively.

Meta-analysis and subgroup analyzes

Pooled effects of carnitine supplementation on serum levels of ALT and AST were estimated in 22 and 23 trials, respectively. Results of random effects model meta-analysis showed that carnitine supplementation could significantly decrease serum levels of ALT (weighted mean difference [WMD] − 10.25 IU/L; 95% CI = − 15.73, − 4.77; $p < 0.001$; test for heterogeneity: $p < 0.001$ and $I^2 = 96.3\%$, Fig. 2) and AST (WMD − 7.85 IU/L; 95% CI = − 11.85, − 3.86; $p < 0.001$; test for heterogeneity: $p = 0.001$ and $I^2 = 55.1\%$, Fig. 3). Subgroup analyzes based on trial duration, carnitine dose, baseline levels of ALT and AST, and health status of included participants were conducted for

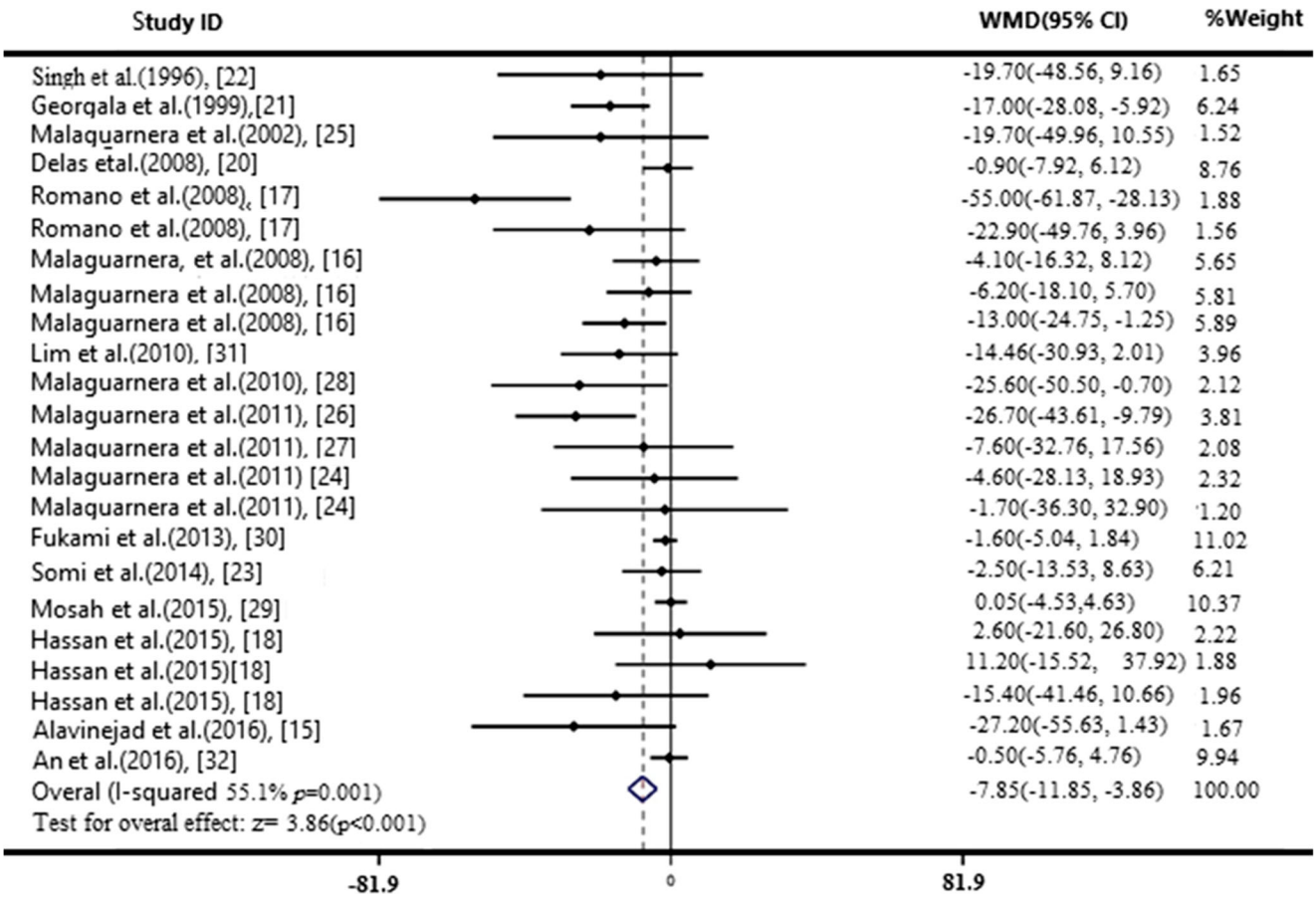

Fig. 3 Forest plot of the random effect model meta-analysis of carnitine supplementation on serum aspartate aminotransferase level (IU/L). *WMD* weighted mean difference

finding possible sources of heterogeneity. The results of subgroup analyzes showed that carnitine could significantly decrease serum AST levels, when the dosage of supplemented carnitine was equal to 2000 mg/day (WMD −22.30 IU/L; 95% CI = −40.15, −4.45; $p = 0.014$) or more than 2000 mg/day (WMD −10.50 IU/L; 95% CI = −16.34, −4.65; $p < 0.001$). However, carnitine at dosages of ≤1000 mg/day (WMD −4.89 IU/L; 95% CI = −9.44, −0.34; $p = 0.035$) or equal to 2000 mg/day (WMD −16.71 IU/L; 95% CI = −29.95, −3.46; $p = 0.013$) successfully exerted its reducing effects on ALT level while doses more than 2000 mg/day did not result in ALT level reduction. The results also showed that carnitine had a significant reducing effect on serum ALT and AST levels when the duration of supplementation lasted at least 3 months or when the patients had increased values of ALT and AST levels. Although carnitine supplementation significantly reduced serum levels of AST and ALT in both the subgroups, this reduction was higher in patients with non-alcoholic steatohepatitis (NASH) and NAFLD than others. The results of subgroup analyzes are summarized in Table 3.

Publication bias

No publication bias was evidenced by the Begg test ($p = 0.20$ for ALT, $p = 0.055$ for AST) and Egger's regression

Table 3 Subgroup analyzes of carnitine supplementation on liver enzyme levels

	No	WMD (95% CI)	*p* within group	*p* heterogeneity	I^2
AST					
Baseline serum AST (U/L)					
< 40	5	2.10 (− 5.62, 1.42)	0.242	0.087	50.8%
40–100	9	− 6.38 (− 11.43, − 1.32)	0.013	0.712	0.0%
> 100	9	− 24.11 (− 33.05, − 15.18)	< 0.001	0.371	7.7%
Trial duration (month)					
< 3	7	− 5.52 (− 11.76, 0.72)	0.083	0.193	30.8%
= 3	10	− 8.00 (− 14.11, − 1.89)	0.010	0.030	51.4%
> 3	6	− 16.83 (− 30.25, − 3.42)	0.014	0.001	76.7%
Carnitine dose (mg)					
≤ 1000	8	− 1.22 (− 3.55, 1.09)	0.301	0.659	0.0%
= 2000	6	− 22.30 (− 40.15, − 4.45)	0.014	0.001	75.0%
> 2000	8	− 10.50 (− 16.34, − 4.65)	< 0.001	0.418	1.4%
Health status					
NAFLD	4	− 13.11 (− 24.93, − 1.30)	0.029	0.178	39.0%
Other diseases	18	− 6.82 (− 11.10, − 2.54)	0.002	0.001	57.9%
ALT					
Baseline serum ALT (U/L)					
< 56	8	− 2.13 (− 4.72, 0.45)	0.106	0.002	69.7%
56–120	9	− 12.16 (− 21.79, − 2.52)	0.013	< 0.001	94.1%
> 120	5	− 23.14 (− 39.58, − 6.70)	0.006	< 0.001	94.2%
Trial duration (month)					
< 3	6	− 3.28 (− 7.94, 1.37)	0.167	0.024	61.2%
= 3	10	− 11.61 (− 22.10, − 1.13)	0.030	< 0.001	98.1%
> 3	6	− 16.33 (− 26.85, − 5.81)	0.002	< 0.001	92.3
Carnitine dose (mg)					
≤ 1000	8	− 4.89 (− 9.44, − 0.34)	0.035	< 0.001	83.0%
= 2000	5	− 16.71 (− 29.95, − 3.46)	0.013	< 0.001	93.6%
> 2000	8	− 10.55 (− 23.36, 2.25)	0.106	< 0.001	97.1%
Health status					
NAFLD	4	− 27.62 (− 39.23, − 16.02)	< 0.001	< 0.001	92.9%
Other diseases	18	− 5.87 (− 9.96, − 1.78)	0.005	< 0.001	91.1%

CI confidence interval, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *WMD* weighted mean differences, *NAFLD* non-alcoholic fatty liver disease

asymmetry test ($p = 0.66$ for ALT, $p = 0.30$ for AST). The funnel plots are depicted in Fig. 4.

Discussion

This meta-analysis was performed to assess the effects of carnitine supplementation on serum aminotransferases (ALT and AST levels) in clinical trials. The results showed that carnitine supplementation can significantly reduce serum levels of ALT and AST in patients with compromised liver function. As the results showed significant evidence of heterogeneity between included studies, subgroup analysis was conducted. The results showed that carnitine could significantly reduce serum levels of AST and ALT when the patients had greater than normal values of these enzymes and when this supplement was consumed at least for 3 months.

As carnitine is synthesized primarily in the liver, patients with liver diseases probably cannot synthesize it in enough quantity and therefore suffer from its deficiency [33]. Carnitine has an essential role in transporting acyl-CoA into the inner membrane of mitochondria for energy production from β-oxidation of fatty acids. Carnitine deficiency can reduce fatty acid oxidation and results in accumulation of fatty acids released from adipose tissue and other tissues in the liver as triglyceride [34]. So, it seems prudent that supplementation with carnitine could improve parameters of liver function including lipoprotein metabolism, insulin resistance, gamma glutamyl transferase (GGT), and ALT and AST levels in patients with chronic liver diseases [28]. Carnitine administration could result in carnitine palmitoyltransferase I (CPT-I) overexpression in hepatocytes, which can reduce insulin resistance induced by lipid deposition in the liver [35]. Several studies showed that carnitine administration can reduce cholesterol and triglyceride synthesis and improve dyslipidemia especially in diabetic patients [36, 37]. Lim et al. in a study on NAFLD patients revealed that carnitine administration can improve the activity of mitochondria by increasing the peripheral blood mitochondrial DNA copy number, which can reduce oxidative stress through scavenging reactive oxygen species (ROS) [31, 38]. An elevation in serum aminotransferase enzymes in chronic liver diseases could increase the risk of death, whereas therapeutic strategies targeting to reduce AST and ALT levels could increase the survival rates in these patients [39]. Another mechanism justifying beneficial effects of carnitine supplementation on liver function in NAFLD patients is probably attributable to its anti-inflammatory and antioxidant properties. Chronic liver diseases could result in hepatocyte apoptosis and proinflammatory cytokine secretion including TNF-α, IL-1b, and IL-6 from Kupffer cells, which can contribute to NAFLD development [40]. One study showed that L-carnitine administration could decrease significantly hs-CRP and TNF-α levels in NASH patients [41]. Oxidative stress is a risk factor for NAFLD progression, and CYP2E1 induction in hepatocytes could result in oxidative stress through lipid peroxidation [42]. Carnitine can scavenge superoxide and hydrogen peroxide radicals and inhibit Fenton reaction by chelating ferrous iron [4]. These results can explain potential reducing effects of carnitine supplementation on ALT and AST levels in patients with chronic liver diseases.

Results of subgroup analysis in the current study showed that the minimum needed dose of carnitine supplements for influencing AST level is 2000 mg/day, while doses more than 2000 mg/day could not influence significantly ALT level.

One important limitation of this study is the lack of enough information about possible confounders including lifestyle habits, dietary intakes, or weight status of participants in studied populations, which can influence the outcomes. Although the number of included trials and total sample size of study populations in this meta-analysis seems to be adequate, heterogeneity of the pathologic conditions of included patients is another limitation of this study.

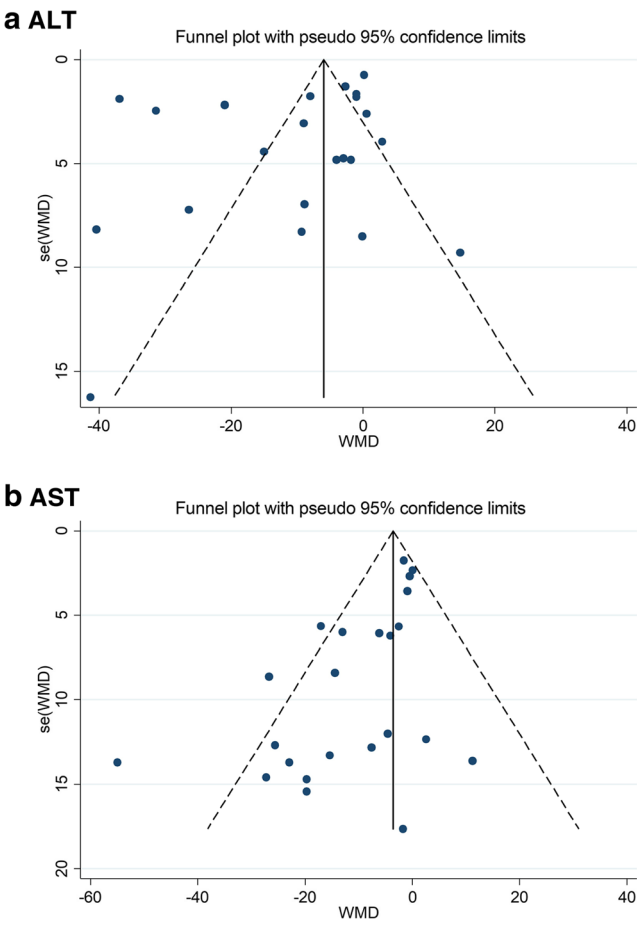

Fig. 4 Funnel plots of liver aminotransferases level changes in patients receiving carnitine supplementation. **a** Alanine aminotransferase (ALT). **b** Aspartate aminotransferase (AST)

In conclusion, results of the current meta-analysis showed that carnitine supplementation can significantly decrease serum levels of AST and ALT and its administration can be recommended as a useful adjuvant treatment strategy for lowering serum level of these aminotransferases in patients suffering from this condition.

Acknowledgements The proposal of this systematic review and meta-analysis was approved in Student Research Committee of Lorestan University of Medical Sciences, Khorramabad, Iran.

Compliance with ethical standards

Conflict of interest EYR, EE, EF, MM, AH, OA, and SS declare that they have no conflict of interest.

Disclaimer The authors are solely responsible for the data and the contents of the paper. In no way, the Honorary Editor-in-Chief, Editorial Board Members, or the printer/publishers are responsible for the results/findings and content of this article.

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