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ORIGINAL ARTICLE

Effect of L-Carnitine Supplementation on Liver Enzymes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background and aim. Possible Hepato-protective effects of L-carnitine have been reported in previous studies. Present study was conducted to systematically review the efficacy of L-carnitine supplementation on liver enzymes.

Methods. The following databases were searched up to December 2018: PubMed, Scopus, ISI Web of Science, and the Cochrane library. Only randomized controlled trials (RCTs) evaluating the effects of L-carnitine supplementation on liver enzymes including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) were included. Pooled effect size measured using random effect model (Dersimonian-Liard).

Results. A total of 16 studies (including 1025 participants) were included in the present meta-analysis. Pooled analysis indicated that L-carnitine supplementation significantly decreased ALT (weighted mean difference (WMD): −10.729 *IU/L*, 95% CI: −13.787, −7.672, p <0.001; I^2 = 95.9%), AST (WMD: −7.149 *IU/L*, 95% CI: −9.202, −5.096, p <0.001; I^2 = 93.5%) and GGT (WMD: −7.395: *IU/L*, 95% CI: −9.171, −5.619, p <0.001; I^2 = 80.1%). Subgroup analysis revealed that effect of L-carnitine supplementation on liver enzymes was not significant in normal weight and healthy subjects. Baseline BMI and health status were the potential source of heterogeneity.

Conclusion. L-carnitine supplementation showed beneficial hepato-protective effects on circulating liver enzymes.

Key Words: L-carnitine, Liver enzymes, Meta-analysis.

Introduction

Alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT) are the enzymes produced mainly in the liver and are commonly measured as part of liver function tests (1). Although they are essential for the human body and they have an important role in amino acid metabolism, elevated levels of these enzymes could be an indicator of inflammation or damage to liver cells or, less likely, damage to other organs that have a role in its production like heart, kidney, brain and muscles (2). Liver injury is a serious complication, demonstrated as different levels of non-alcoholic fatty liver disease, which could consequently increase the risk of mortality from cardiovascular diseases or cancer (3). Although different lifestyle modifications were reported to be practical approach against hepatic damage. Still, weight loss is the only approved treatment for non-alcoholic fatty liver disease (NAFLD) (4). However, the protective role of certain supplementations has also been noted recently.

L-carnitine is a conditionally essential amino-acid synthesized endogenously from lysine or methionine in the liver, kidney, and brain or can be obtained from certain foods (5). It functions as a transporter of long-chain fatty acids into mitochondria, therefore, it is an important contributor to cellular energy metabolism (6,7), and its

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deficiency could impair the use of fat as fuel and decreases energy availability in vital organs, especially in the liver (8). Therefore, it is logical to assume carnitine deficiency is associated with liver injury as it has been reported in several studies. Moreover, the protective role of L-carnitine against various hepatic disorders such as hepatotoxicity and steatohepatitis has been suggested in many studies (9).

Since the liver enzymes are the main parameters through which the function of the liver is measured (10), to clarify the role of L-carnitine, its effect on these enzymes should be noted. Previous animal studies showed that L-carnitine could exert hepato-protective effects in different models against acetaminophen induced hepatotoxicity (11); acute hepatic encephalopathy alone or combined (12); or even prevent liver damage caused by high cholesterol diet (13). In a study cirrhotic hepatocellular carcinoma patients supplemented with L-carnitine showed improvement of liver functions following a particular treatment with sever hepatic damage (14). However, there is controversy in this area as several studies have reported that L-carnitine administration had a significant effect on lowering liver enzymes (15−17), while there are other studies that did not support such a claim (18−20). To our knowledge, no meta-analysis has been performed to address this issue. Hence, we conducted this systematic review and meta-analyses to examine the effect of L-carnitine supplementation on ALT, AST, and GGT.

Methods

Present meta-analysis reported based on the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) statement guideline (21). The PICOS-model (22), where the acronym PICOS stands for population (all individuals except children under 18 years old and pregnant and lactating women), intervention (carnitine supplementation), comparison (studies which had control group), outcome (studies that reported ALT, AST or GGT) and study design were randomized controlled trial (RCT) was used.

Search Strategy

A throughout search was conducted in PubMed, Scopus, ISI Web of Science and Cochrane library from inception to December 2018. The merger of MeSH and non-MESH terms were as follows: ''carnitine'', OR ''l-carnitine'' OR ''levo-carnitine'' OR ''acetyl carnitine'' OR ''acetyl-l-carnitine'' OR ''ACAL'' AND ''Intervention Studies'' OR ''intervention'' OR ''controlled trial'' OR ''randomized'' OR ''randomised'' OR ''random'' OR ''randomly'' OR ''placebo'' OR ''assignment''. We hand searched all reference lists of eligible articles, related reviews, and meta-analyses to prevent missing any relevant studies. Unpublished documents and grey literature like conference papers, theses, and patents were not included.

Eligibility Criteria

The included studies in this meta-analysis were as follows: (1) randomized control trials (RCT), (2) only executed on adult population and (3) reported one of the following measures; ALT, AST or GGT. Articles were excluded if (1) they were study design except RCT, (2) had studies the effects of L-Carnitine along with other interventions (3) had lack of sufficient data for the outcomes of interest in individuals and (4) studies carried out with less than two weeks' follow-ups.

Data Extraction

Two independent researchers (M. A., E. Gh.) conducted the study selection whereas a chief investigator (SS-b) was also present to resolve any controversies. In case of data deficiency, we contacted the accountable author to acquire the necessary data. The following data were obtained from each study: first author's name, year of publication, study location, study duration, gender, mean age and mean body mass index (BMI) of participants, study design, health status of study population, number of participants in each group, dose of L-carnitine supplementation and ALT, AST, GGT levels before and after intervention.

Data Synthesis

Mean and standard deviation (SD) of ALT, AST and GGT were used for determination of pooled effect, otherwise standard errors (SE) were converted to SD according to the formula of $SE^*\sqrt{n}$. This Meta-analysis was conducted to compare the pooled estimates of liver enzymes before and after the administration of L-Carnitine supplementation. In case of high heterogeneity between studies, a random-effect model (Dersimonian-Liard) as well as subgroup analysis was used to pool the effect sizes. WMD were applied for measurement of mean differences. In brief, WMD use the crude unit of variables and expanding results could be more practical; however other methods for calculating mean difference did not use the exact effect and standardize them; we cannot report unit in regard of them therefore it seems that this could be more practical. Subgroup analysis for duration and carnitine dosage selected based on median of studies; BMI stratified based on published guidelines for overweight and obesity; different types of carnitine and also different health status were chosen for possible source of heterogeneity; the age of 45 years old selected based on previous studies for defining middle age. All statistical analyses were done using Stata software version 12 (StataCorp. College Station, Texas, USA). $p < 0.05$ was considered as statistically significant.

Results

Study Selection

Out of 9680 provided articles in initial search, 3073 duplicated studies excluded. After screening of title and abstract 6566 unrelated studies discarded due to primary evaluation of inclusion criteria: Unrelated title (n = 5835), animal study (n = 648), letter, short survey and note (n = 46) and review and book section (n = 37). Consequently 41 studies remained and after full text screening, 25 studies were excluded based on the following criteria: a) performed on children (n = 1) (23), b) administration of L-carnitine orotate (n = 1) (24), c) reported different unit (mg/dL) of interest outcomes (25), d) studies that enough information was not stated in them (n = 22) (26–47). Studies with orotate administration as L-carnitine orotate excluded from this review due to potential effect of orotic acid on increasing liver enzymes (48). Finally, 16 studies met all inclusion criteria. The PRISMA flow diagram of search process is depicted in Figure 1.

Quality Assessment

We assessed the quality of the included studies by using Cochrane scoring system. It consists of 7 criteria to assess the risk of the bias which are as follows: random sequence

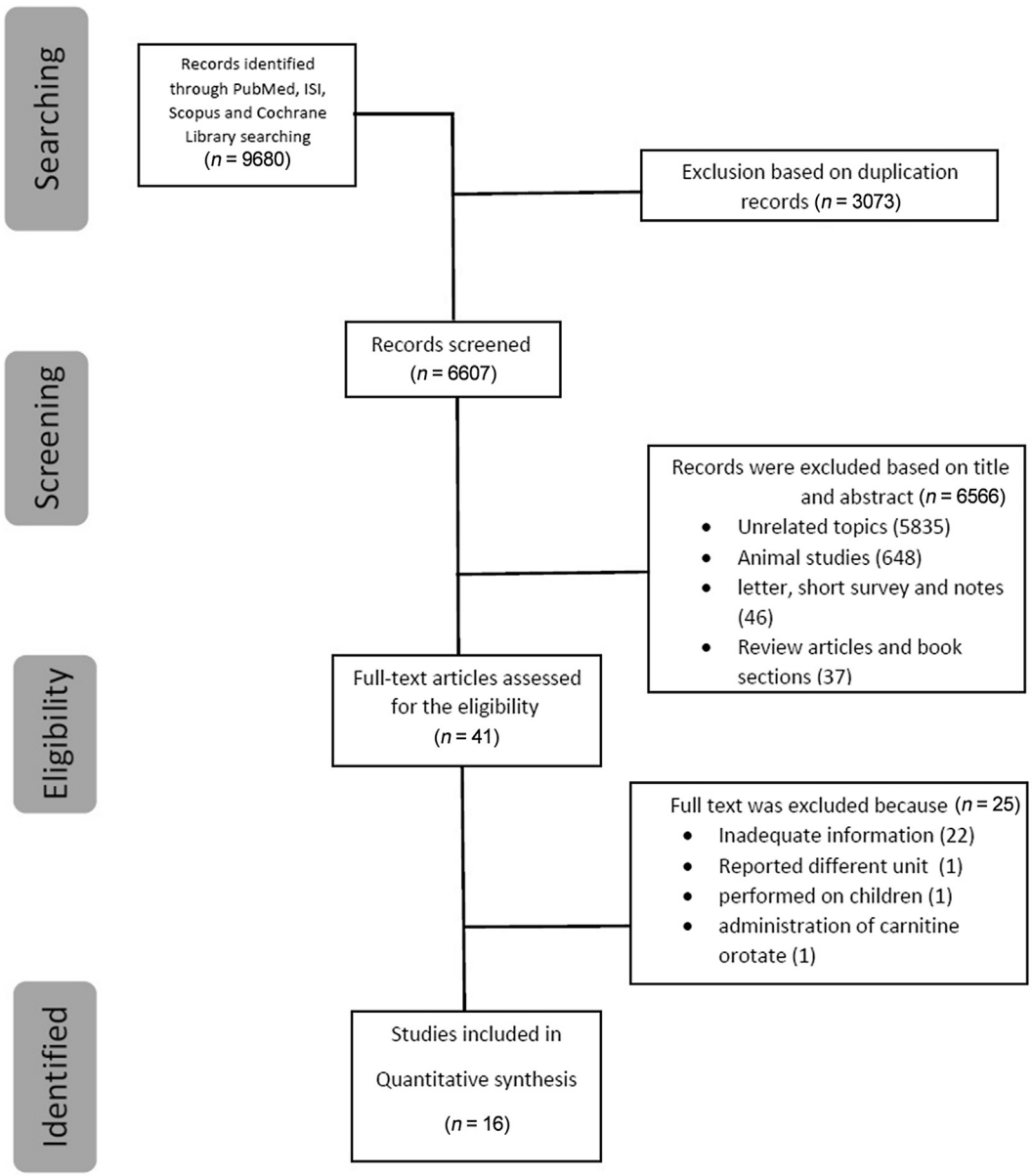

Figure 1. Study flow chart.

generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. Three variables, yes, no, and unclear could be given to each aforementioned item, which are interpreted as high risk, low risk and unknown risk respectively. Random allocation of participants was mentioned in all included trials. Nevertheless, 10 trials described the method of random sequence generation (15,16,18,48−54). Allocation concealment reported in 9 studies (16−18,49,51−53,55,56). Moreover, 4 trials had high risk of bias regarding blinding of participants, personnel and outcome assessors (19,49,50,54). Selective reporting considered as low risk in 5 trials (15,18,51,53,55). All of studies showed low risk of bias based on incomplete outcome data and other potential threats to validity. Details of risk of bias assessment are described in Table 1.

Study Characteristics

Eventually, 16 studies with 1025 participants were included. Included studies were published between 1996 and 2018. The follow-up period ranged from 2 weeks to 12 months. The sample size of the included studies ranged from 10−115 participants. All of studies were parallel randomized clinical trial. Rout of L-carnitine administration has done orally in all of the studies. Selected studies enrolled subjects with suspected acute myocardial infarction (56), diabetes (15), cirrhotic patients (17), nonalcoholic steatohepatitis (49), hypothyroidism (18), hyperthyroidism (57), hemodialysis patients (19), hepatic encephalopathy (16,50,52), chronic hepatitis C (49,50,54) and healthy subjects (20,53,55). Included studies carried out in different countries such as Italy (16,17,48−50,52,54,57), Iran (15,53), Japan (19,20), Croatia (55), South Korea (18) and India (56). Some studies enrolled only males (20,53) and females (57) and the rest of included studies involved both genders (15−19,48−50,52,54−56). In addition, the studies performed in subjects with different baseline BMI; six studies carried out in subjects under 25 kg/m^2 (17−19,53,55), 5 studies over than 25 kg/m^2 (15,20,48−50,54) and 5 study did not report BMI (16,50,52,56,57). Type of carnitine administration were Acetyl L-carnitine (16,17,51,52) and L-carnitine (15,18−20,48−50,53−57) among included studies. Characteristics of included studies are abstracted in Table 2.

Meta-Analysis

Effect of L-carnitine supplementation on AST. Overall, 16 clinical trials with 22 arms (521 cases and 504 control subjects) evaluated the effect of L-carnitine supplementation on AST. Pooled effect size from random effect model showed a significant lowering effect of L-carnitine supplementation on AST (−7.149 IU/L, 95% CI: −9.202, −5.096, $p < 0.001$). There was significant heterogeneity between studies ($I^2 = 93.5\%$, $p < 0.001$) (Figure 2). Subgroup analyses were performed based on baseline BMI, participants' condition (healthy, unhealthy subjects and patients with liver disorders), dose of L-carnitine (<2 vs. ≥2 g/d), study duration (≤12 and more than 12 weeks), age (≤45 and >45) and type of L-carnitine (L-carnitine and Acetyl-Carnitine). Subgroup analysis based on baseline BMI and health status could explain potential between-study heterogeneity. As, heterogeneity decreased to non-significant value and the effect also is significant. Subgroup analysis based on dose, type of carnitine, age and study duration showed no significant differences between

Table 1. Cochrane risk of bias of included studies

Study	Reference	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Alavinejad et al.	(15)	L	U	L	L	L	L	U
An et al.	(18)	L	L	L	L	L	L	U
Benvenga et al.	(57)	U	U	L	L	L	U	U
Delas et al.	(55)	U	L	L	L	L	L	U
Fukami et al.	(19)	U	U	H	H	L	U	U
Malaguarnera et al.	(16)	L	L	L	L	L	U	U
Malaguarnera et al.	(50)	L	U	H	H	L	U	U
Malaguarnera et al.	(49)	L	U	H	H	L	U	U
Malaguarnera et al.	(51)	U	L	L	L	L	U	U
Malaguarnera et al.	(52)	L	L	L	L	L	U	U
Malaguarnera et al.	(48)	L	L	L	L	L	U	U
Malaguarnera et al.	(17)	L	L	L	L	L	L	U
Mohtadinia et al.	(53)	L	L	L	L	L	L	U
Odo et al.	(20)	U	U	L	L	L	U	U
Romano et al.	(54)	L	U	H	H	L	U	U
Singh et al.	(56)	U	L	L	L	L	U	U

L, low risk of bias; H, high risk of bias; U, unknown risk of bias.

Table 2. Characteristics of included studies

Author (location, year)	Study design	Population	Gender	Number (case/ control)	Intervention mean (range) age (years)	Intervention mean BMI (Kg/m^2)	Duration (weeks)	Intervention/ control	Liver enzymes (IU/l)				
										Intervention		Control	
									Type	Basal	Change from baseline	Basal	Change from baseline
Alavinejad et al. (Iran, 2016) (15)	Parallel (double-blind)	Diabetic Patients	M/F	28/26	60	28.6	13	L-carnitine (750 mg/ day)/Placebo	AST ALT	122.7 ± 13.6 124 ± 11.3	−26.4 ± 9.03 −41.9 ± 7.79	125.3 ± 14 120 ± 10.8	0.8 ± 8.40 −5±6.92
An et al. (South Korea, 2016) (18)	Parallel (double-blind)	Hypothyroidism	M/F	28/25	49	24.7	12	L-carnitine (1980 mg/day)/ Placebo	AST ALT	21.3 ± 5 18.9 ± 13.4	−0.4 ± 4.03 −1±8.73	22.3 ± 5.5 18 ± 7.7	0.1 ± 3.44 0 ± 4.81
Benvenga et al. (Italy, 2001) (57)	Parallel (double-blind)	Iatrogenic Hyperthyroidism	F	10/10	48.3	Nr	4	L-carnitine (2 g/day)/Placebo	AST ALT GGT	21.48 ± 1.96 30.48 ± 2.48 18.47 ± 2.67	−0.32 ± 1.24 1.01 ± 1.56 −1.31 ± 1.69	15.81 ± 1.98 30.64 ± 1.99 14.07 ± 2	4.95 ± 1.23 11.81 ± 1.21 4.65 ± 1.26
Benvenga et al. (Italy, 2001) (57)	Parallel (double-blind)	Iatrogenic Hyperthyroidism	F	10/10	43.4	Nr	4	L-carnitine (4 g/day)/Placebo	AST ALT GGT	21.61 ± 1.81 17.47 ± 1.6 25.3 ± 2.76	−2.32 ± 1.15 −0.72 ± 1.01 −3.91 ± 1.75	15.81 ± 1.98 30.64 ± 1.99 14.07 ± 2	4.95 ± 1.23 11.81 ± 1.21 4.65 ± 1.26
Benvenga et al. (Italy, 2001) (57)	Parallel (double-blind)	Iatrogenic Hyperthyroidism	F	10/10	42.2	Nr	8	L-carnitine (2 g/day)/Placebo	AST ALT GGT	22.79 ± 1.75 13.82 ± 1.93 16.42 ± 2.44	−0.57 ± 1.15 2.21 ± 1.17 −0.88 ± 1.56	15.81 ± 1.98 30.64 ± 1.99 14.07 ± 2	4.95 ± 1.23 11.81 ± 1.21 4.65 ± 1.26
Benvenga et al. (Italy, 2001) (57)	Parallel (double-blind)	Iatrogenic Hyperthyroidism	F	10/10	40.1	Nr	8	L-carnitine (4 g/day)/Placebo	AST ALT GGT	21.43 ± 1.47 20.65 ± 2.49 20.15 ± 2.09	−1.86 ± 0.93 1.42 ± 1.56 −1.47 ± 1.32	15.81 ± 1.98 30.64 ± 1.99 14.07 ± 2	4.95 ± 1.23 11.81 ± 1.21 4.65 ± 1.26
Delas et al. (Croatia, 2008) (55)	Parallel (double-blind)	Healthy Sedentary Population	M/F	18/12	23.1	22.7	2	L-carnitine (2 g/day)/Placebo	AST ALT	18.7 ± 3.3 13.2 ± 3.5	−0.3 ± 2.64 2.2 ± 6.07	19 ± 3.1 12.1 ± 4.4	0.6 ± 1.93 3.2 ± 2.97
Fukami et al. (Japan, 2013) (19)	Parallel (open-label trial)	Hemodialysis Patients	M/F	32/38	68	22.3	26	L-carnitine (900 mg/ day)/Placebo	AST ALT	14.8 ± 6.7 12.8 ± 9.4	−2.1 ± 4.60 −3±5.76	15.4 ± 5.8 12.8 ± 5.5	−0.5 ± 4.04 −0.3 ± 4.95
Malaguarnera et al. (Italy,2010) (48)	Parallel (double-blind)	Nonalcoholic Steatohepatitis	M/F	36/38	47.9	26.6	24	L-carnitine (2 g/day) plus "ad libitum" diet/placebo plus "ad libitum" diet	AST ALT GGT	128.1 ± 13.9 110.2 ± 15.6 104.1 ± 17.2	−71.7 ± 10.9 −58.4 ± 10.15 −37.6 ± 10.44	124.2 ± 12.8 112.8 ± 13.1 98.2 ± 18.2	−46.1 ± 13.54 −37.4 ± 8.57 −20.4 ± 11.94
Malaguarnera et al. (Italy,2011) (50)	Parallel (open-label trial)	Chronic hepatitis C	M/F	30/27	47.6	27.1	54	L-carnitine (4 g/day) plus (1.5 μg/kg per week) Peg-IFN-α 2b plus (800-1200 mg) Ribavirin/placebo plus Peg-IFN-α (1.5 μg/kg per week) plus ribavirin (800-1200 mg)	AST ALT	145 ± 44.2 182.1 ± 46.2	−108.8 ± 34.81 −137.9 ± 36.12	136 ± 41.1 174.1 ± 42.2	−76.8 ± 30.22 −112.3 ± 31.27
Malaguarnera et al. (Italy, 2002) (49)	Parallel (open-label trial)	Chronic Hepatitis C	M/F	14/11	56.8	26	26	L-carnitine (2 g/day) plus IFNα (3 million IU three times a week)/IFNα (3 million IU three times a week)	AST ALT	110 ± 86 186 ± 99	−59.5 ± 58.05 −108.2 ± 70.41	114 ± 79 163 ± 108	−39.8 ± 54.64 −66.9 ± 65.44
Malaguarnera et al. (Italy, 2008) (17)	Parallel (double-blind)	Cirrhotic patients	M/F	60/55	48	24.8	13	acetyl-L-carnitine (4 g/day)/Placebo	AST ALT	111.5 ± 10.7 71 ± 40	−12.1 ± 6.54 −8±24.08	105.2 ± 10.6 68 ± 44	−12.6 ± 12.72 −6.2 ± 27.26
Malaguarnera et al. (Italy, 2011) (16)	Parallel (double-blind)	Minimal hepatic encephalopathy	M/F	33/33	37–65	Nr	13	acetyl-L-carnitine (4 g/day)/placebo	AST ALT	140.7 ± 13.8 117.4 ± 16	−15.2 ± 9 −66.2 ± 11.06	136.8 ± 23.5 90.2 ± 14.3	−6.2 ± 14.19 −34.8 ± 8.98
Malaguarnera et al. (Italy, 2011) (52)	Parallel (double-blind)	Severe hepatic encephalopathy	M/F	30/30	37–64	Nr	13	acetyl-L-carnitine (4 g/day)/placebo	AST ALT	119.2 ± 13.1 106.7 ± 15.7	−17 ± 8.14 −10.7 ± 9.73	114.2 ± 24.5 136.3 ± 31	−9.4 ± 14.72 −13.6 ± 19.36

Author (location, year)	Study design	Population	Gender	Number (case/ control)	Intervention mean (range) age (years)	Intervention mean BMI (Kg/m^2)	Duration (weeks)	Intervention/ control	Liver enzymes (IU/l)				
										Intervention		Control	
									Type	Basal	Change from baseline	Basal	Change from baseline
Malaguarnera et al. (Italy, 2011) ((51)	Parallel (double-blind)	Mild hepatic encephalopathy	M/F	31/30	40–66	Nr	13	acetyl-L-carnitine (4 g/day)/placebo	AST	98.6 ± 12.8	−9.2 ± 7.83	105.3 ± 12.4	−4.6 ± 8.09
									ALT	111.5 ± 10.7	−12.1 ± 6.54	105.2 ± 10.6	−12.6 ± 12.72
Malaguarnera et al. (Italy, 2011) (51)	Parallel (double-blind)	Moderate hepatic encephalopathy	M/F	30/30	40–66	Nr	13	acetyl-L-carnitine (4 g/day)/placebo	AST	124.4 ± 22.4	−9.6 ± 13.46	154.9 ± 10.6	−7.9 ± 6.45
									ALT	140.7 ± 13.8	−15.2 ± 9	136.8 ± 23.5	−6.2 ± 14.1
Mohtadinia et al. (Iran, 2013) (53)	Parallel (double-blind)	Healthy male football players	M	7/7	20.7	21.2	3	L-carnitine (2 g/ day)/placebo	AST	35.3 ± 4.9	−7.4 ± 3.06	27.4 ± 3.9	−5.4 ± 2.44
Mohtadinia et al. (Iran, 2013) (53)	Parallel (double-blind)	Healthy male football players	M	7/7	21.3	19.9	3	L-carnitine (2 g/day) plus L-Glutamine (2 g/day)/L-Glutamine (2 g/day)	AST	40.4 ± 17.4	−14.1 ± 11.22	29.6 ± 10	−5.7 ± 7.74
Odo et al. (Japan, 2013) (20)	Parallel (double-blind)	Healthy Volunteers	M	5/5	44.4	26.6	4	L-carnitine (500 mg/ day) plus motivation training/placebo plus motivation training	AST	22.4 ± 4.2	−0.2 ± 2.6	22.4 ± 5.4	−2.2 ± 3.27
									ALT	28.2 ± 9.7	−0.8 ± 5.82	20.6 ± 6.3	−2.4 ± 3.98
									GGT	51.4 ± 20.5	−1.8 ± 19.47	32.6 ± 9.7	−1.2 ± 6.31
Odo et al. (Japan, 2013) (20)	Parallel (double-blind)	Healthy Volunteers	M	6/5	43.3	25.8	4	L-carnitine (500 mg/ day)/Placebo	AST	26.5 ± 4.7	0.7 ± 5.77	23.2 ± 3.7	2.2 ± 4.09
									ALT	39.3 ± 16.3	3 ± 13.13	23.6 ± 8.4	8.4 ± 11.99
									GGT	46.2 ± 24.7	1 ± 15.21	39.2 ± 12.1	18.8 ± 29.72
Romano et al. (Italy, 2007) (54)	Parallel (open-label trial)	Chronic Hepatitis C	M/F	35/35	50.1	25.8	54	L-carnitine (2 g/day) plus IFNα (3 million IU three times a week) plus ribavirin (1 g/day)/IFNα (3 million IU three times a week) plus ribavirin (1 g/day)	AST	125 ± 46.2	−76.5 ± 28.53	116 ± 49.3	−53.6 ± 29.61
									ALT	162 ± 49.2	−94.2 ± 30.57	156 ± 47.4	−67.8 ± 29.91
Singh et al. (India, 1996) (56)	Parallel (double-blind)	Suspected acute myocardial infarction	M/F	51/50	49.2	Nr	4	L-carnitine (2 g/ day)/placebo	AST	170 ± 15.8	−45.7 ± 9.71	172.2 ± 17.6	−26 ± 10.56

All such values expressed as mean ± SD.

AST, aspartate aminotransferase; ALT, alanine transaminase; F, female; GGT, Gamma-Glutamyl Transferase; M, male; Nr, not reported.

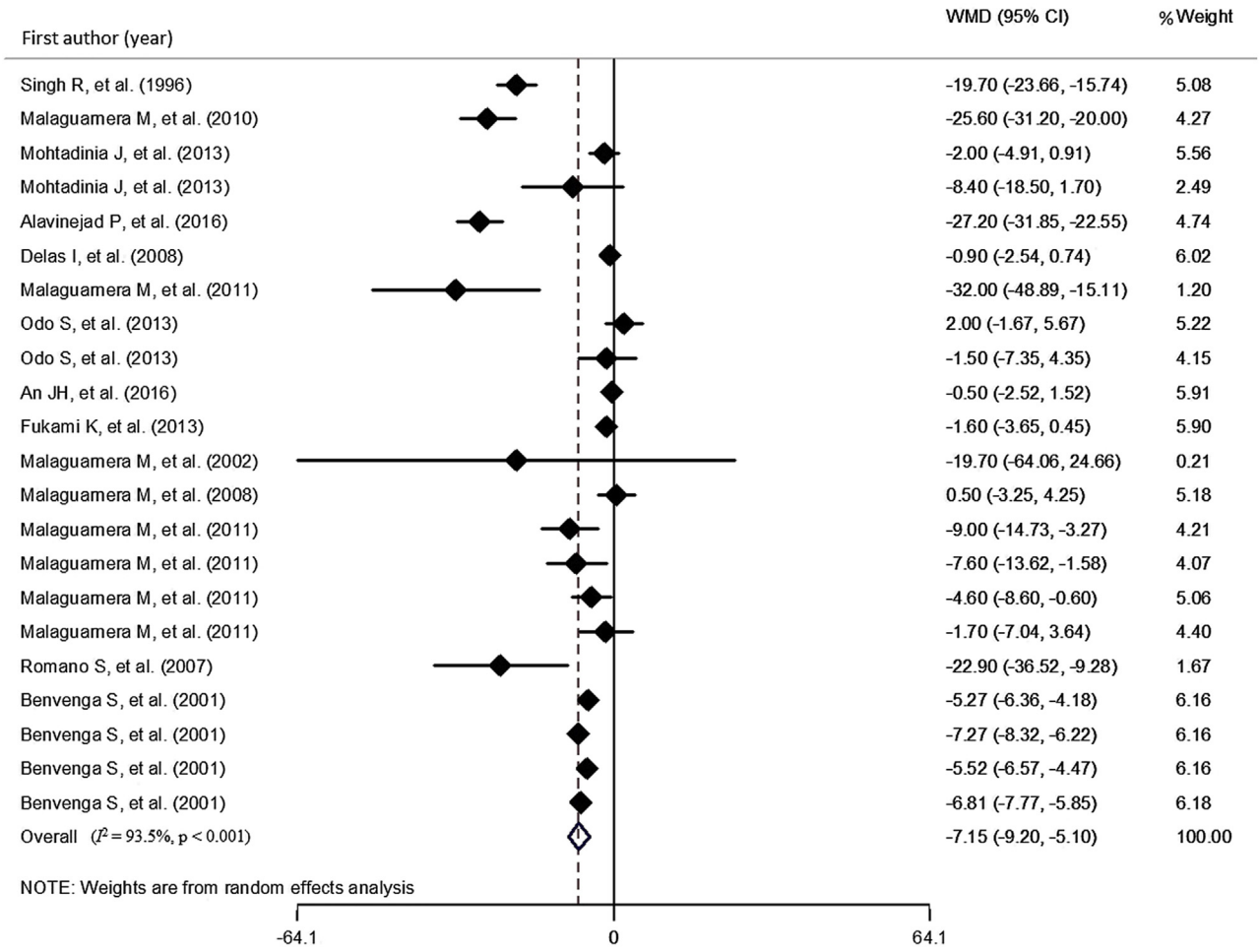

Figure 2. Effect of L-carnitine supplementation on AST.

subgroups (Table 3). However, subgroup analysis based on BMI showed that subjects with BMI lower than 25, without significant heterogeneity (I^2 = 0.0%, p = 0.59). In addition, only in unhealthy subjects and patients with liver disorders AST significantly decreased following L-carnitine supplementation.

Effect of L-carnitine supplementation on ALT. The effect of the L-carnitine supplementation on ALT was investigated in 15 trials with 18 arms (456 cases and 440 control subjects). Overall, meta-analysis showed that ALT decreased significantly following L-carnitine supplementation (−10.729 IU/L, 95% CI: −13.787, −7.672, p <0.001. Due to a significant heterogeneity between studies (I^2 = 95.9%, p < 0.001) (Figure 3), subgroup analysis based on baseline BMI and health status was done. Subgroup analysis revealed that L-carnitine supplementation significantly decreased ALT in unhealthy subjects and patients with liver disorders; however, in healthy subjects did not show any significant effect. In all other subgroups regarding dosage, BMI, intervention period, type of L-carnitine and age, association remained significant as shown in Table 3.

Effect of L-carnitine supplementation on GGT. The effect of the L-carnitine supplementation on GGT was examined in seven arms from three studies with 176 subjects. Overall, current meta-analysis showed significant effects of L-carnitine supplementation on GGT (−7.395: IU/L, 95% CI: −9.171, −5.619, p <0.001). There was significant heterogeneity among studies (I^2 = 80.1%, p <0.001) (Figure 4). Subgroup analysis revealed that both doses (≤2 g and >2 g) decreased GGT serum level significantly. However, L-carnitine supplementation did not improve GGT serum level in healthy subjects as shown in Table 3.

Sensitivity Analysis and Publication Bias

The sensitivity analyses indicated that the results were not excessively influenced by any of the studies (Supplementary Figures 1−3). There was also no evidence of publication bias for studies examining the effect of L-

Table 3. Subgroup analysis to assess the effect of L-carnitine supplementation on liver enzymes

Characteristics	No. of trial	WMD[a] (95% CI)	*p*	*P* For heterogeneity	I^2 (%)	*p* for between subgroup heterogeneity
AST						
Total	22	−7.149 (−9.202, −5.096)	0.000	0.000	93.5	
Baseline BMI						0.000
<25 kg/m^2	6	−1.063 (−2.037, −0.090)	0.032	0.594	0.0	
≥25 kg/m^2	7	−11.586 (−13.873, −9.29)	0.000	0.000	95.7	
Dosage						0.000
≤2 g	14	−4.680 (−5.258, −4.101)	0.000	0.000	95.2	
>2 g	8	−6.701 (−7.372, −6.031)	0.000	0.000	76.0	
Intervention Duration (Weeks)						0.226
≤12	11	−5.448 (−5.911, −4.985)	0.000	0.000	93.1	
>12	11	−6.327 (−7.672, −4.982)	0.000	0.000	94.3	
Type of Study Population						0.000
Healthy	5	−0.909 (−2.196, 0.379)	0.167	0.276	21.7	
Unhealthy subjects	9	−6.099 (−6.579, −5.619)	0.000	0.000	96.2	
Liver Disorders	8	−6.930 (−8.862, −4.999)	0.000	0.000	89.7	
Type of Carnitine						0.052
L-carnitine	17	−5.634 (−6.082, −5.186)	0.000	0.000	94.8	
Acetyl-Carnitine	5	−3.506 (−5.606, −1.406)	0.001	0.034	61.6	
Age						0.208
≤45	10	−5.422 (−5.898, −4.947)	0.000	0.000	89.0	
>45	12	−6.206 (−7.330, −5.082)	0.000	0.000	95.4	
Baseline Activity of AST						0.000
<50	11	−5.071 (−5.525, −4.616)	0.000	0.000	90.6	
≥50	11	−11.562 (−13.189, −9.936)	0.000	0.000	93.7	
ALT						
Total	19	−10.729 (−13.787, −7.672)	0.000	0.000	95.9	
Baseline BMI						0.000
<25 kg/m^2	7	−1.822 (−3.562, −0.083)	0.040	0.829	0	
≥25 kg/m^2	4	−23.64 (−26.154, −21.130)	0.000	0.000	94.8	
Dosage						0.000
≤2 g	11	−9.837 (−10.536, −9.138)	0.000	0.000	96.8	
>2 g	8	−11.688 (−12.424, −10.952)	0.000	0.000	93.8	
Intervention Duration (Weeks)						
≤12	9	−10.848 (−11.380, −10.317)	0.000	0.000	94.7	
>12	10	−9.379 (−11.060, −7.697)	0.000	0.000	97	
Type of Study Population						0.000
Healthy	3	−0.612 (−3.452, 2.228)	0.673	0.624	0	
Unhealthy subjects	7	−10.851 (−11.381, −10.322)	0.000	0.000	97.6	
Liver Disorders	9	−14.563 (−16.804, −12.322)	0.000	0.000	93.5	
Type of Carnitine						0.704
L-carnitine	14	−10.696 (−11.212, −10.180)	0.000	0.000	96.1	
Acetyl-Carnitine	5	−11.231 (−13.940, −8.521)	0.000	0.000	96.1	
Age						0.262
≤45	8	−10.820 (−11.359, −10.281)	0.000	0.000	94.9	
>45	11	−9.914 (−11.404, −8.424)	0.000	0.000	96.7	
Baseline Activity of ALT						0.000
<50	9	−10.035 (−10.560, −9.510)	0.000	0.000	93.6	
≥50	10	−20.053 (−21.99, −18.106)	0.000	0.000	95.9	
GGT	7	−7.395 (−9.171, −5.619)	0.000	0.000	80.1	
Type of Study Population						0.000
Healthy	2	−5.421 (−20.644, 9.802)	0.485	0.320	0	
Unhealthy subjects	4	−6.467 (−7.092, −5.842)	0.000	0.000	76	
Liver Disorders	1	−17.20 (−22.306, −12.094)	0.000	−	−	
Dosage						0.094
≤2 g	5	−6.080 (−6.968, −5.192)	0.000	0.001	80.0	
>2 g	2	−7.140 (−8.006, −6.274)	0.000	0.006	86.5	

[a]Weighted mean difference.

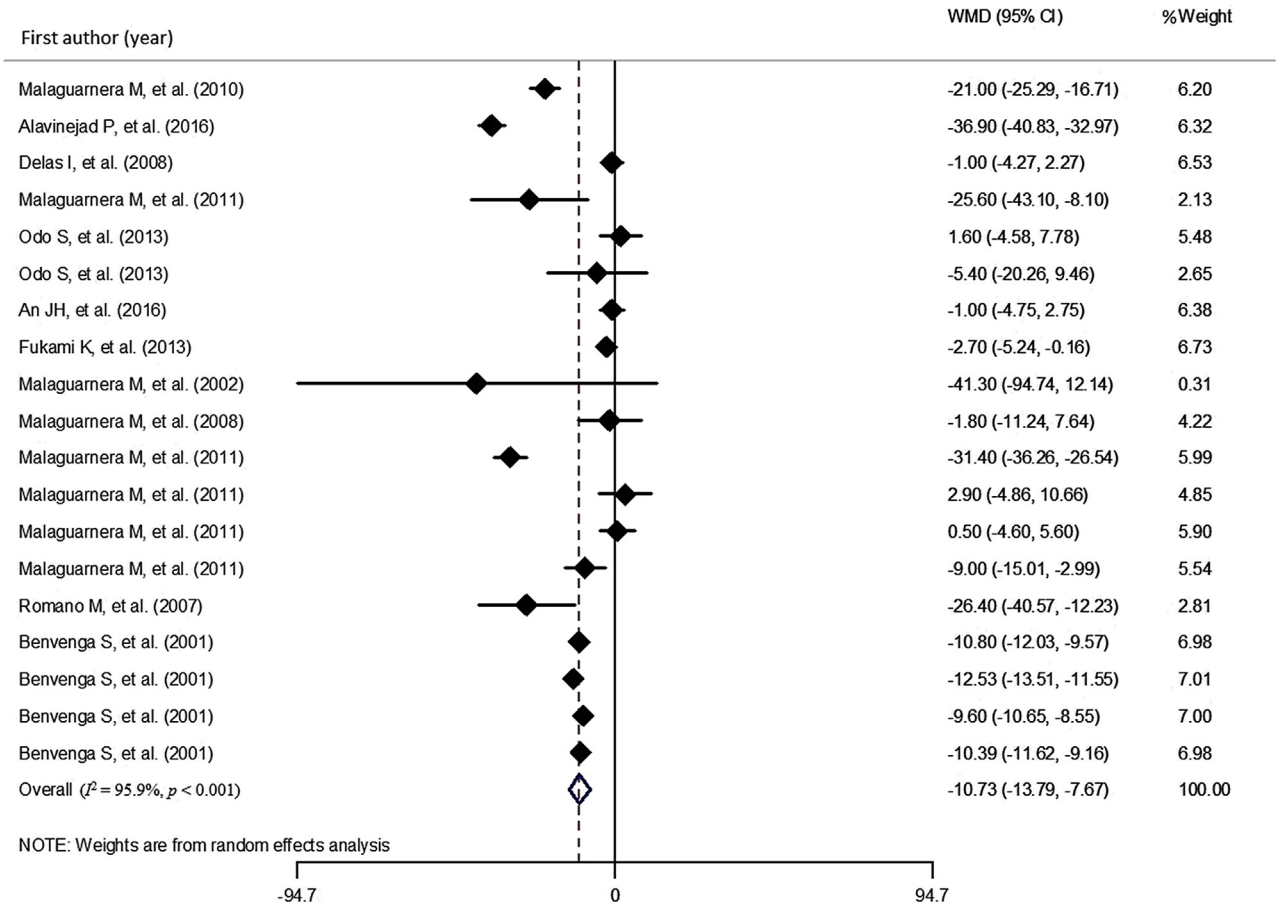

Figure 3. Effect of L-carnitine supplementation on ALT.

carnitine on AST ($p = 0.410$, Egger's test), ALT ($p = 0.980$, Egger's test) and GGT ($p = 0.366$, Egger's test) (Supplementary Figure 4).

Discussion

In the current study, we found a significant reduction in AST, ALT and GGT by L-carnitine supplementation based on random-effects model. However, there was an evidence of between-study heterogeneity in this regard. Dividing studies by participants' health condition explained between-study variation and revealed a lowering effect of L-carnitine supplementation in subjects with unhealthy condition or liver disorders. To the best of our knowledge, current systematic review and meta-analysis is the first to summarize the effect of L-carnitine supplementation on liver enzymes.

Beneficial effects of L-carnitine supplement intake on lipid profile, inflammatory biomarkers and oxidative stress have been shown in previous studies (33,58,59). L-carnitine is involved in long-chain fatty acids transportation from cytoplasm to mitochondria in liver cells and consequently increases the oxidation of these fatty acids (60). Therefore, L-carnitine supplementation may affect liver function. Recent clinical trials have assessed the effects of L-carnitine supplementation on liver parameters by considering its enzymes. However, those findings are conflicting and no study, until now, has presented a definite conclusion in this regard.

Chronic inflammation in the liver results in cell death which could induces repair and remodeling responses. Liver has enormous regeneration potential; during remodeling responses several biomolecules are generated and released into the bloodstream mainly from damaged/dying cells, tissue matrix and infiltrated immune cells. This includes, liver enzymes and other proteins such as AST, ALT and GGT (61,62). Based on our findings, L-carnitine supplementation resulted in a significant reduction in AST, ALT and GGT levels. In line with our findings, previous studies have shown favorable effects of L-carnitine supplementation on liver, particularly in subjects with liver disorders. In a review paper, Felker et al. (63), concluded that L-carnitine is involved in the regulation of valproic acid-induced hepatotoxic processes, and intake of L-carnitine supplements had protective effects against

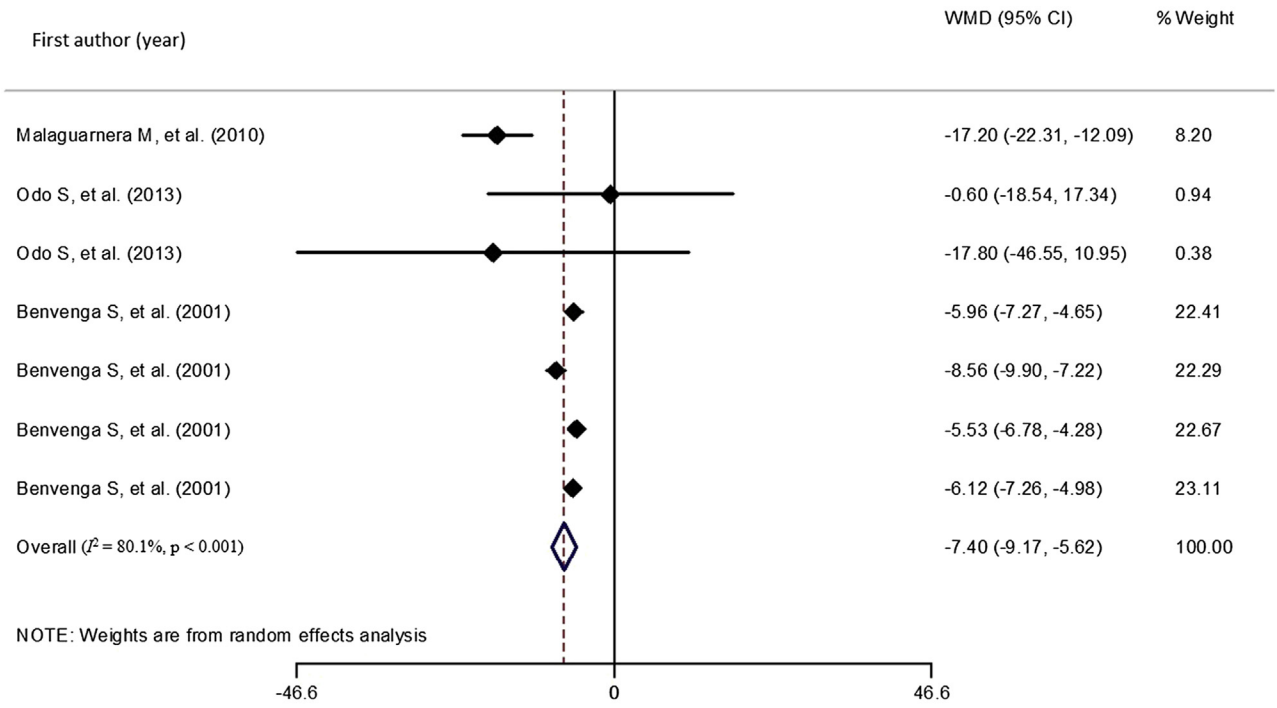

Figure 4. Effect of L-carnitine supplementation on GGT.

hepatotoxicity. In another study, L-carnitine supplementation increased tissue survival time and survival rate after hepatic cell damage (64). In an experimental study, L-carnitine administration resulted in preservation of liver enzymes (ALT, AST and GGT) after inducing hepatic cell injury (65). Among RCTs included in the current systematic review and meta-analysis, most studies showed a significant reduction in liver enzymes following L-carnitine supplementation, but limited number of studies indicated no significant effect. These conflicting results may be due to different quality of included RCTs or different health condition of subjects participated in RCTs.

As seen in previous studies and the current meta-analysis, L-carnitine supplementation is more effective on patients with liver disorders. It might be explained by elevated levels of liver enzymes in these patients who may have better response to L-carnitine supplementation. However, in the current study, when we divided RCTs by baseline levels of liver enzymes (normal vs. elevated), effects of L-carnitine supplementation on these enzymes were similar in both subgroups. Limited number of studies on healthy subjects is another reason for lack of significant effect of L-carnitine supplementation on liver enzymes in these subjects.

The real mechanisms underlying the lowering effect of L-carnitine supplementation on liver enzymes are unclear, but we can assume that L-carnitine is involved in in β-oxidation of free fatty acids (FFAs) and therefore decreases the accumulation of FFAs-induced lipotoxic metabolites which might contribute to mitochondrial dysfunction and insulin resistance (66). Mitochondrial dysfunction in liver cells is a predictor for liver disorders and increase in levels of liver enzymes (66,67). Furthermore, beneficial effect of L-carnitine on liver enzymes can be mediated by inflammation (68,69). Inflammatory biomarkers have a role in liver dysfunction and elevated levels of liver enzymes (69,70). Anti-inflammatory properties of L-carnitine might improve liver function and decrease liver enzymes levels (71–73).

Safety

High doses of L-carnitine may increase the serum levels of trimethylamine-N-oxide (TMAO) which can adversely increase the risk of blood pressure and atherosclerosis (74–76). In an experimental study, injected TMAO could significantly increase the pro-inflammatory cytokines in the aorta and enhance blood pressure in rat models (77). Elevated level of TMAO could be used as biomarkers to predict prevalence of cardiovascular diseases (78). Moreover, several meta-analyses showed that TMAO is an independent risk factor for CVD and mortality risks (79–81). A mechanistic role for TMAO for CVD development may be through promoting aortic endothelial cell activation, and elevation of inflammatory gene signaling (82).

The strength of our systematic review and meta-analysis is the first to summarize findings on the effect of L-carnitine supplementation on liver enzymes. In addition, Egger's test provided no evidence of substantial publication bias in the current meta-analysis. However, some limitations should be

considered. Both the doses of L-carnitine and the duration of the interventions varied across the included studies. However, in subgroup analysis, we tried to separate studies based on dose and duration of intervention, we cannot entirely exclude these variations. Furthermore, RCTs included participants with different health conditions. Because our subgroup analysis revealed significant effects of L-carnitine supplementation in studies that included participants with unhealthy condition or liver disorders, prospective studies are warranted in subjects with specific condition to ascertain these findings. Different methods used for measuring liver enzymes across included studies, lack of controlling for different confounders and presence of high risk of bias (based on Cochrane criteria) in some studies are another limitation for current meta-analysis.

In conclusion, combined data from interventional studies revealed a significant reduction in AST, ALT and GGT levels after oral supplementation with L-carnitine. This significant effect was also seen in subjects with unhealthy conditions or liver disorders, but not healthy individuals.

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