Complementary Therapies in Medicine 48 (2020) 102273

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

The effects of carnitine supplementation on clinical characteristics of patients with non-alcoholic fatty liver disease: A systematic review and meta-analysis of randomized controlled trials

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ARTICLE INFO

Keywords:
Carnitine
Liver function
Lipid profile
Insulin resistance
Nonalcoholic fatty liver disease
Meta-analysis

ABSTRACT

Objective: The beneficial effects of carnitine supplementation on nonalcoholic fatty liver disease are unclear. We conducted a systematic review and meta-analysis to evaluate the effects of carnitine supplementation on liver function, lipid profile, body mass index, body weight, and homeostasis model assessment of insulin resistance in patients with nonalcoholic fatty liver disease.

Methods: A comprehensive search of PubMed, Web of Science, Scopus, Cochrane Library, and Google Scholar databases were performed. Only randomized placebo-controlled human studies that examined the effects of carnitine supplementation on liver function, lipid profile, body mass index, body weight, and homeostasis model assessment of insulin resistance up to September 2019 were included. Fixed effects or random-effects models were applied to compute the pooled effect size. Heterogeneity assessments were performed using Cochran's Q test and I-squared statistics. The quality of the studies was assessed using the Jaded scale.

Results: A total of 5 articles were selected, including 334 individuals (167 in control and 167 in intervention groups). The results demonstrated that carnitine supplementation significantly reduced homeostasis model assessment of insulin resistance (HOMA-IR) (WMD: −0.91; 95 % CI: −1.11, −0.72; $p < 0.001$, $I^2 = 0.0$ %) and the levels of aspartate aminotransferase (AST) (WMD: −16.62; 95 % CI: −28.11, −5.14; IU/l; $p = 0.005$, $I^2 = 93.5$ %), alanine aminotransferase (ALT) (WMD: -33.39; 95 % CI: −45.13, −21.66; IU/l; $p < 0.001$, $I^2 = 93.4$ %), and triglycerides (TG) (WMD: −22.13; 95 % CI: −38.91, −5.34; mg/dl; $p = 0.01$; $I^2 = 0.0$ %). However, the results of the pooled effect size did not show any significant effect of carnitine supplementation on body mass index (BMI) (WMD: 0.07; 95 % CI: −0.15, 0.29; $p = 0.55$; $I^2 = 0.0$ %), body weight (WMD: −0.28; 95 % CI: −2.23, 1.68; $p = 0.78$; $I^2 = 45.7$ %), the levels of gamma-glutamyl transferase (γGT) (WMD: −11.31; 95 % CI: −24.35, 1.73; IU/l; $p = 0.09$, $I^2 = 61.1$ %), cholesterol (WMD: −13.58; 95 % CI: −46.77, 19.60; mg/dl; $p = 0.42$; $I^2 = 94.9$ %), high-density lipoprotein-cholesterol (HDL-C) (WMD: 1.36; 95 % CI: −0.96, 3.68; mg/dl; $p = 0.25$; $I^2 = 64.7$ %), and low density lipoprotein-cholesterol (LDL-C) (WMD: −14.85; 95 % CI: −45.43, 15.73; mg/dl; $p = 0.34$; $I^2 = 96.4$ %).

Conclusions: This analysis shows that carnitine supplementation for patients with nonalcoholic fatty liver disease demonstrates a reduction in AST, ALT, TG levels and HOMA-IR. However, no significant effect of carnitine supplementation was observed on BMI, body weight, the levels of γGT, TC, HDL-cholesterol and LDL-cholesterol.

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; γGT, gamma-glutamyltransferase; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low- density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; BMI, body mass index

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https://doi.org/10.1016/j.ctim.2019.102273
Received 12 July 2019; Received in revised form 8 November 2019; Accepted 26 November 2019
Available online 29 November 2019

1. Introduction

More than 100 types of liver disease have been identified, among which Non-alcoholic Fatty Liver Disease (NAFLD) is the most prevalent liver diseases in the world.[1,2] The pathological and clinical manifestations of NAFLD include simple steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and these may eventually lead to hepatocellular carcinoma.[1,2] According to the "two-hit" hypothesis,[3] steatosis can manifest as the first hit and subsequently be a predictive factor for liver fibrosis in patients with NAFLD.[4] Therefore, steatosis is an active factor in the development of NAFLD.[4] As a result, any efforts in reducing steatosis in patients with liver disease may improve their liver function.

Carnitine (3-hydroxy-4-*N, N, N*-trimethylaminobutyric acid) is a quaternary amine that acts as a necessary ingredient for the function of our body. Carnitine can be obtained from animal sources such as dairy products, meat, poultry, and fish.[5,6] Endogenous carnitine is synthesised in kidneys and liver from methionine, lysine, ascorbic acid, iron, niacin, and vitamin B6.[7] L- carnitine is one of the derivatives of carnitine with extensive bioactivity.[8] The role of L-carnitine in lipid metabolism is well understood. It facilitates the transfer of long-chain fatty acids from the mitochondrial membrane and subsequently activates the β-oxidation of fatty acids.[9]

Several studies have shown the beneficial roles of carnitine in some liver diseases. However, the findings remain controversial. A previous meta-analysis revealed the improvement in steatosis and NASH following L-carnitine supplementation.[10] L-carnitine supplementation at a dose of 750 mg per day for three months in patients with NAFLD significantly reduced the serum levels of liver transaminases (AST and ALT). Nonetheless, no significant reduction was observed in the serum level of cholesterol and triglycerides (TG).[11] Besides, the administration of carnitine-orotate complex at a dose of 300 mg per day for three months showed an improvement of the liver function enzymes levels (ALT and γGT), total bilirubin and lipid profile (cholesterol and TG) in patients with fatty liver.[12]

The inconsistent results may be due to the differences in study design, dosage and type of the carnitine supplementation, and the characteristics of the subjects in the different studies. This systematic review and meta-analysis aim to determine the effect of carnitine supplementation on liver function, lipid profile, body mass index, body weight, and homeostasis model assessment of insulin resistance in nonalcoholic fatty liver disease patients conducted in randomised placebo-controlled human studies.

2. Methods

2.1. Search strategies

This systematic review and meta-analysis were constructed based on PRISMA guidelines.[13] We carried out a systematic literature search of PubMed, Web of Science, Scopus, Cochrane Library, and Google Scholar databases to extract the randomised clinical trials (RCTs) published until September 2019. The following MeSH terms were included in the title, keywords, abstract, and text, i.e. patients ["fatty liver" OR "liver steatosis" OR "non-alcoholic fatty liver disease" OR "nonalcoholic fatty liver disease" OR "fatty liver, nonalcoholic" OR "liver, nonalcoholic fatty" OR "NAFLD" OR "non-alcoholic steatohepatitis" OR "steatohepatitides, nonalcoholic" OR "steatohepatitis, nonalcoholic" OR "NASH"], intervention ["carnitine" OR "l-carnitine" OR "bicarnesine" OR "acetyl-L-carnitine" OR "l-acetylcarnitine" OR "levocarnitine" OR "vitamin BT"], and outcomes ["aspartate aminotransferase (AST)" OR "alanine aminotransferase (ALT)" OR "gamma-glutamyltransferase (γGT)" OR "bilirubin" OR "albumin" OR "total-cholesterol (TC)" OR " triglycerides (TG)" OR "LDL-cholesterol" OR "LDL-C" OR "HDL-cholesterol" OR "HDL-C" OR "BMI" OR "body mass index" OR "body mass" OR "body weight" OR "weight" OR "weight loss" OR "weight reduction" OR "weight change" OR " insulin resistance " OR "homeostasis model assessment of insulin resistance (HOMA-IR)"]. A manual search was also performed based on the references list of the included articles. Only articles published in the English language were included in this study.

2.2. Study selections

The RCTs that have examined the effects of carnitine supplementation on liver function tests (ALT, AST, and γGT), lipid profile (TG, total cholesterol, HDL-C, and LDL-C), BMI, body weight, and HOMA-IR were included in the study by two independent authors using the following criteria: 1) original articles, 2) RCTs of human studies 3) patients with nonalcoholic fatty liver disease, 4) intervention group received carnitine supplement or carnitine supplement plus other nutrients, 5) reported mean changes in liver function tests, lipid profile, BMI, body weight, and/or HOMA-IR with standard deviation (SD) and 95 % confidence intervals (CIs) in the intervention and control groups. Studies with insufficient data for analysis or without control or placebo group were excluded from the study.

2.3. Data extraction and quality assessment

After identifying all the articles, two independent authors (AM, MZ) excluded any duplicate articles based on the title and abstract. Then, the full-text of the articles were retrieved and assessed for its quality using the Jadad scale (Table 1). Jaded scale consists of five criteria, namely randomisation procedures, explanation the proportionality of the randomisation method, blindness, the procedure of blinding, and the statement and cause of withdrawals.[14] In the case of disagreement between the two authors, the third author (BN) was consulted to resolve the problem. The following information from the included studies was extracted and categorised: the first name of the authors, publication year, the place of study, participants' health status, study design, group sample size, sex, age, the supplement (type and dosage), and study duration. The mean, standard deviation (SD), and 95 % CIs were also extracted for liver function tests (AST, ALT, and γGT), lipid profile (TG, total cholesterol, HDL-C, and LDL-C), BMI, body weight, and HOMA-IR for both groups (intervention and control group).

2.4. Subgroup analysis

The following potential moderator variables were used for a subgroup analysis including; trial duration (≤ 3 months vs. $>$ 3 months), participant's health status (NAFLD vs. NASH), carnitine supplement dose ($\leq$ 500 mg vs. $>$ 500 mg), quality assessment of study based on Jaded score (≤ 3 vs. $>$ 3), and type of carnitine supplement (L-carnitine vs. Carnitine orotate complex).

2.5. Data synthesis and statistical analysis

In this study, the effects of carnitine supplement on liver function test (AST, ALT, and γGT), lipid profile (TG, total cholesterol, HDL-C, and LDL-C), BMI, body weight, and HOMA-IR were estimated. We used the mean difference (MD), SD, and 95 % CIs to assess the effects of carnitine supplementation on liver function, lipid profile tests, BMI, body weight, and HOMA-IR. Cochran's Q test (at $p < 0.05$ level of significance) and I-squared statistics (I^2) were exerted among included studies for assessment of heterogeneity. I^2 that is larger than 50 percent represents heterogeneity.

Fixed effects or random-effects models were applied to compute the pooled effect size with 95 % confidence interval (CI). Subgroup analysis was performed to determine the source of heterogeneity including trial duration, type of carnitine supplement, the dose of carnitine, quality of articles based on the Jaded score, and participants' health status. To assess for possible publication bias, Egger's [15] and Begg's [16] tests were used. A $p < 0.05$ was indicated as statistically significant. All the

Table 1
Characteristics of included studies.

Authors (Ref)/ Publication Year	Country	participants health status	Study design	Sample size (control / intervention)	Sex (M/F)	Intervention (name and daily dose)	Trial Duration	Biomarkers	Age (control / intervention) (Years)	Jaded score
Alavinejad et al (2016)[11]	Iran	Non-alcoholic fatty liver disease patients (NAFLD)	Randomized double blind control trial	26/28	M/F	L-carnitine 750 mg	3 months	AST, ALT TG, TC	59 ± 9/ 60 ± 5	3
Somi et al (2014)[19]	Iran	Non-alcoholic fatty liver disease patients (NAFLD)	Randomized placebo-controlled trials	40/40	M/F	L-carnitine 500 mg	24-week	AST, ALT, BMI, body weight	41.1 ± 8.3/ 40.3 ± 7	1
Malaguarnera et al (2010)[17]	Italy	Non-alcoholic Steatohepatitis Patients (NASH)	Randomized double blind control trial	38/ 36	M/F	L-carnitine 2000mg	24 weeks	AST, ALT, γ GT Albumin, TC, TG, LDL-C, HDL-C, BMI, HOMA-IR	47.8 ± 5.8 / 47.9 ± 5.4	5
Bae et al (2015)[18]	Korea	Non-alcoholic fatty liver disease patients (NAFLD)	Randomized double blind control trial	39/39	M/F	Carnitine-orotate complex (300 mg carnitine ortate)	12-week	AST, ALT γ GT, TG, HDL-C, LDL-C, BMI, body weight, HOMA-IR	52 ± 9.4 / 50.6 ± 9.3	4
Hong et al (2014)[12]	Korea	Non-alcoholic fatty liver disease patients (NAFLD)	Randomized double blind control trial	24/24	M/F	Carnitine orotate complex (300 mg carnitine ortate)	12 weeks	AST, ALT, γ GT Bilirubin, TC, TG, LDL-C, HDL-C, BMI, HOMA-IR	52.0 ± 9.6 / 51.5 ± 9.4	3

AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; γGT, Gamma-glutamyltransferase; TG, triglycerides; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low- density lipoprotein cholesterol; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance.

statistical analyses in this study were performed with STATA version 14.0 (Stata Corp, College Station, TX).

3. Results

3.1. Included studies

From the 673 included studies that were evaluated by the two independent authors, a total of 247 duplicated articles were excluded. Out of the remaining 426 studies, a further evaluation showed that a total of 4 studies met the study criteria and were included in the final analysis. After reviewing the reference lists of the included studies, an extra study was identified, giving a total of 5 studies in the meta-analysis. The flowchart of the identification of eligible studies is shown in Fig. 1.

3.2. Study characteristics

Table 1 shows the characteristics of the studies. From a total of five studies, four of them were randomized double-blind control trials while one was randomized placebo-controlled trials. All these studies (n = 5) examined the effects of carnitine supplementation on AST and ALT but the effects on TG and BMI were examined by 4 studies and the effects on γGT, total cholesterol, HDL-C, LDL-C levels and HOMA-IR were only examined by 3 studies. Only two studies assessed the effects of carnitine supplementation on body weight change. The five studies were carried out in different countries including Italy,[17] Korea,[12,18] and Iran [11,19] between the year 2010 and 2016. The total number of participants from all the studies was 334 individuals, including 167 individuals in the control group and 167 individuals in the intervention group. The duration of studies ranged from 12 weeks to 24 weeks. The dosage of carnitine supplementation varied from 300 to 2000 mg per day. L-carnitine and carnitine orotate complex were used in all the studies. Quality assessment based on the Jadad scale showed that only one study received a score of 5 and a score of 4 respectively. Two studies scored 3, and one study scored 1.

3.3. The effects of carnitine supplementation on liver function tests

The results of random effect models of the five effect sizes in the current meta-analysis illustrated that carnitine supplementation significantly reduced AST levels (WMD: −16.62; 95 % CI: −28.11, −5.14; IU/l; p = 0.005) (Fig. 2 and Table 2). The above results remained unchanged in the subgroup analysis, except for studies with the Jaded score ≤3 (WMD: −2.7; 95 % CI: −7.54, 2.13; IU/l), carnitine orotate complex supplementation (WMD: −13.59; 95 % CI: −35.59, 8.42; IU/l), carnitine dose ≤ 500 mg (WMD: −9.18; 95 % CI: −20.76, 2.40; IU/l), NAFLD patients (WMD: −14.32; 95 % CI: −28.95, 0.32; IU/l), and trial duration > 3 months (WMD: -14.15; 95 % CI: −36.78, 8.49; IU/l) (Table 3).

The results of meta-analysis of the five effect sizes in this study showed that carnitine supplementation significantly reduced ALT levels (WMD: −33.39; 95 % CI: −45.13, −21.66; IU/l p < 0.001) (Fig. 3 and Table 2) but the results of subgroup analysis remained unchanged. Pooling results of three studies illustrated no significant effects of carnitine supplementation on γGT levels after administration of carnitine supplementation (WMD: −11.31; 95 % CI: −24.35, 1.73; IU/l; p = 0.09) (Fig. 4 and Table 2). The results in subgroup analysis remained unchanged except for studies with duration > 3 months (WMD: −17.20; 95 % CI: −22.31, −12.09; IU/l) using the dosage of carnitine supplementation > 500 mg/day (WMD: −17.20; 95 % CI: −22.31, −12.09; IU/l), L-carnitine supplementation (WMD: −17.20; 95 % CI: −22.31, −12.09; IU/l), NASH patients (WMD: −17.20; 95 % CI: −22.31, −12.09; IU/l), and Jaded score > 3 (WMD: −17.16; 95 % CI: −22.11, −12.22; IU/l) (Table 3).

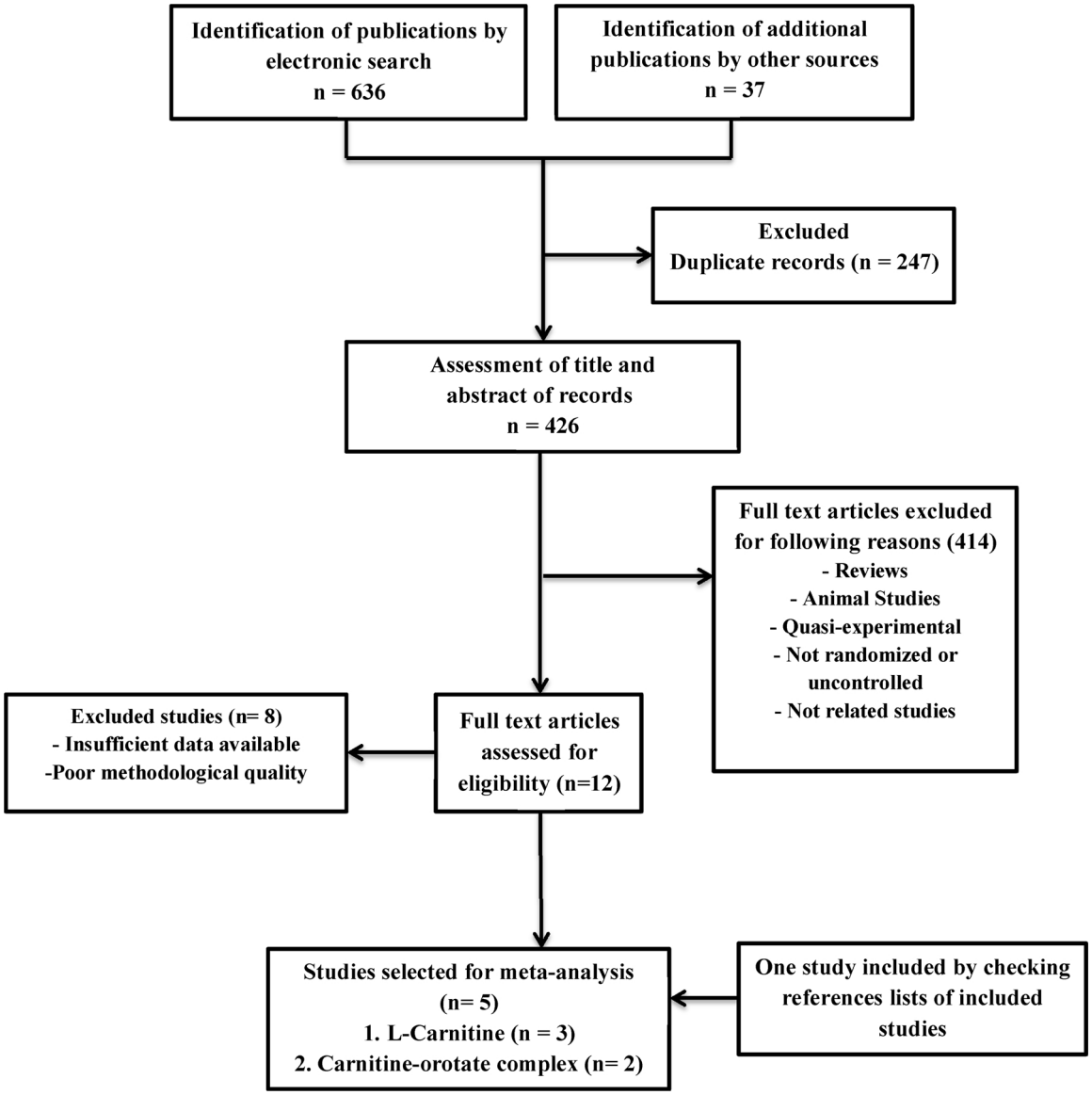

Fig. 1. Flowchart of identification of eligible trials to include in the meta-analysis.

3.4. The effects of carnitine supplementation on lipid profile tests

Results of random-effects model from the meta-analysis of 4 effect sizes demonstrated that supplementation of carnitine reduced TG levels (WMD: −22.13; 95 % CI: −38.91, −5.34; mg/dl; p = 0.01) (Fig. 5 and Table 2). However, the subgroup analysis results were changed except for studies with duration > 3 months (WMD: −32.74; 95 % CI: −55.45, −10.03; mg/dl), NASH patients (WMD: −32.74; 95 % CI: −55.45, −10.03; mg/dl), and Jaded score > 3 (WMD: −21.90; 95 % CI: −40.13, −3.66; mg/dl) (Table 3). Besides, results of 3 effect sizes in the meta-analysis illustrated no significant effects of carnitine supplementation on the total cholesterol levels (WMD: −13.58; 95 % CI: −46.77, 19.60; mg/dl; p = 0.42) (Fig. 6 and Table 2). The results remained the same in the subgroup analysis except for studies with duration > 3 months (WMD: -44.47; 95 % CI: −54.77, −34.17; mg/dl), and NASH patients (WMD: −44.47; 95 % CI: −54.77, −34.17; mg/dl) (Table 3).

Lastly, carnitine supplementation also did not have any effects on HDL-C levels, as demonstrated in the meta-analysis of 3 effect sizes (WMD: 1.36; 95 % CI: −0.96, 3.68; mg/dl; p = 0.25) (Fig. 7 and Table 2). However, the subgroup analysis results remained the same except for studies with duration > 3 months, NASH patients, and carnitine supplementation dose > 500 mg, and L-carnitine supplementation (WMD: 3.10; 95 % CI: 1.61, 4.59; mg/dl) (Table 3). Finally, the pooled findings of 3 studies with administration of carnitine supplementation did not show any significant changes in LDL-C levels (WMD: −14.85; 95 % CI: −45.43, 15.73; mg/dl; p = 0.34) (Fig. 8 and Table 2) and the results of subgroup analysis did not change except for studies with duration > 3 months, NASH patients, carnitine supplementation dose > 500 mg, and L-carnitine supplementation (WMD: −44.85; 95 % CI: −54.84, −34.86; mg/dl) (Table 3).

3.5. The effects of carnitine supplementation on BMI, body weight, and HOMA-IR

The pooled findings for four random-effect models demonstrated that carnitine supplementation did not have any effects on BMI (WMD: 0.07; 95 % CI: −0.15, 0.29; P = 0.55) (Fig. 9 and Table 2). Results of the subgroup analysis remained the same (Table 3). carnitine supplementation did not have any effects on body weight, as demonstrated in the meta-analysis of 2 effect sizes (WMD: −0.28; 95 % CI: −2.23, 1.68; mg/dl; p = 0.78) (Fig. 10 and Table 2). In meta-analysis of three effect

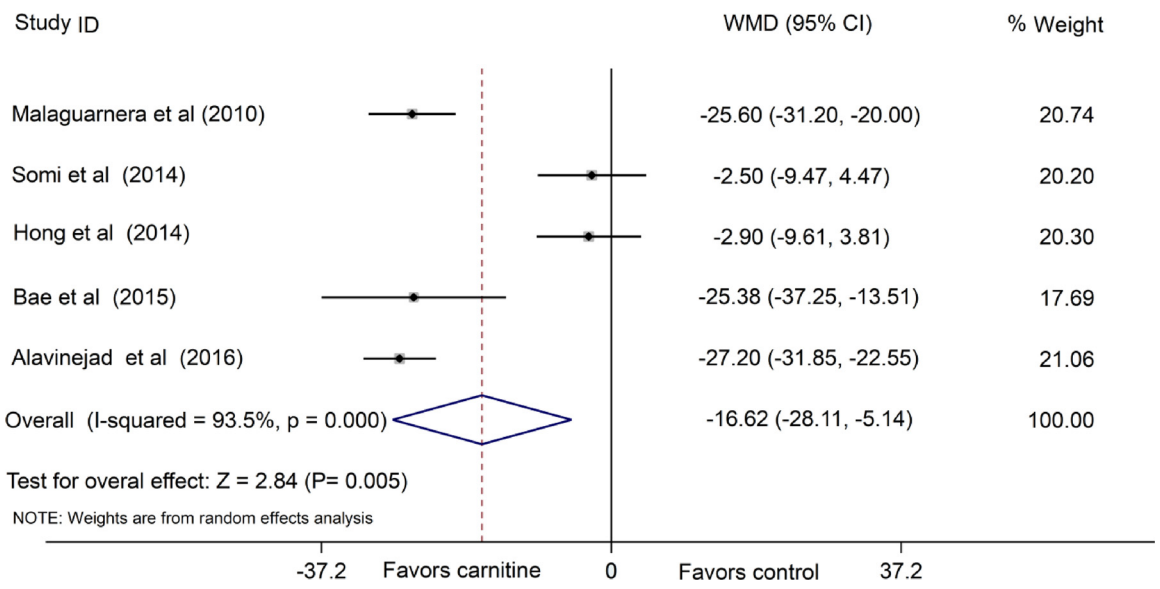

Fig. 2. Forest plot of AST change outcome.

sizes, carnitine supplementation significantly reduced HOMA-IR (WMD: −0.91; 95 % CI: −1.1, −0.72; p < 0.001) (Fig. 11 and Table 2). The results in the subgroup analysis remained unchanged except in the studies with duration ≤ 3 months (WMD: −0.21; 95 % CI: −2.11, 1.68), studies conducted among NAFLD patients (WMD: −0.21; 95 % CI: −2.11, 1.68), carnitine supplementation dose ≤ 500 mg(WMD: −0.21; 95 % CI: −2.11, 1.68), studies with Jaded score ≤ 3 (WMD: −0.40; 95 % CI: −3.10, 2.30), and the use of carnitine orotate complex (WMD: −0.21; 95 % CI: −2.11, 1.68) (Table 3).

3.6. Sensitivity analyses

The results of the sensitivity analysis remained consistent with the estimated pooled effect size for the effect of carnitine supplementation on AST, ALT, TC, LDL-C, HDL-C, body weight, and BMI (Table 4). However, the authors showed that the pooled WMD for γGT was a remarkable change between the pre- (−11.31; 95 % CI, −24.35, 1.73) and post-sensitivity pooled WMD (−17.16; 95 % CI, −22.11, −12.22) excluding the study by Hong et al. (2014); for TG indicated the pre- (−22.13; 95 % CI, −38.91, −5.34) and post-sensitivity pooled WMD (−9.34; 95 % CI, −34.26, 15.59) excluding the study by Malaguarnera et al. (2010); and for HOMA-IR indicated similar findings between the pre- (−0.91; 95 % CI, −1.10, −0.72) and post-sensitivity pooled WMD (−0.21; 95 % CI, −2.11, 1.68) excluding the study by Malaguarnera et al. (2010).

3.7. Publication bias

Based on Egger's regression tests, no publication bias was reported for the effect of carnitine supplementation on AST (p = 0.53), ALT (p = 0.69), γGT (p = 0.52), TG (p = 0.49), total cholesterol (p = 0.35), HDL-C (p = 0.26), LDL-C (p = 0.86), BMI (p = 0.35), and HOMA-IR (p = 0.17). Furthermore, based on Begg's tests, no publication bias was reported for the effect of carnitine supplementation on body weight (p = 0.32).

4. Discussion

The current systematic review and meta-analysis demonstrated that carnitine supplementation significantly reduced AST, ALT, and TG levels and HOMA-IR but did not affect BMI, body weight, the levels of γGT, TC, HDL-cholesterol and LDL-cholesterol in nonalcoholic fatty liver disease patients. To our best knowledge, this is the first meta-analysis of RCTs to assess the effect of carnitine supplementation on liver function, lipid profile, BMI, body weight, and HOMA-IR of patients with nonalcoholic fatty liver disease.

Table 2
The effects of carnitine supplementation on liver function tests (AST, ALT, and γ-GT), lipid profile (TG, TC, HDL-C, and LDL-C), BMI, body weight, and HOMA-IR in patients with nonalcoholic fatty liver disease.

Variables	Number of effect sizes	Weighted mean difference	CI 95 %	P value	Heterogeneity	
					I^2 (%)	P- value heterogeneity
AST	5	−16.62	−28.11, −5.14	0.005	93.5	< 0.001
ALT	5	−33.39	−45.13, −21.66	< 0.001	93.4	< 0.001
γGT	3	−11.31	−24.35, 1.73	0.09	61.1	0.08
TG	4	−22.13	−38.91, −5.34	0.01	0.0	0.55
TC	3	−13.58	−46.77, 19.60	0.42	94.9	< 0.001
HDL-C	3	1.36	−0.96, 3.68	0.25	64.8	0.06
LDL-C	3	−14.85	−45.43, 15.73	0.34	96.4	< 0.001
BMI	4	0.07	−0.15, 0.29	0.55	0.0	0.54
Body weight	2	−0.28	−2.23, 1.68	0.78	45.7 %	0.18
HOMA-IR	3	−0.91	−1.11, −0.72	< 0.001	0.0	0.75

AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; γGT, Gamma-glutamyltransferase; TG, triglycerides; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low- density lipoprotein cholesterol; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance.

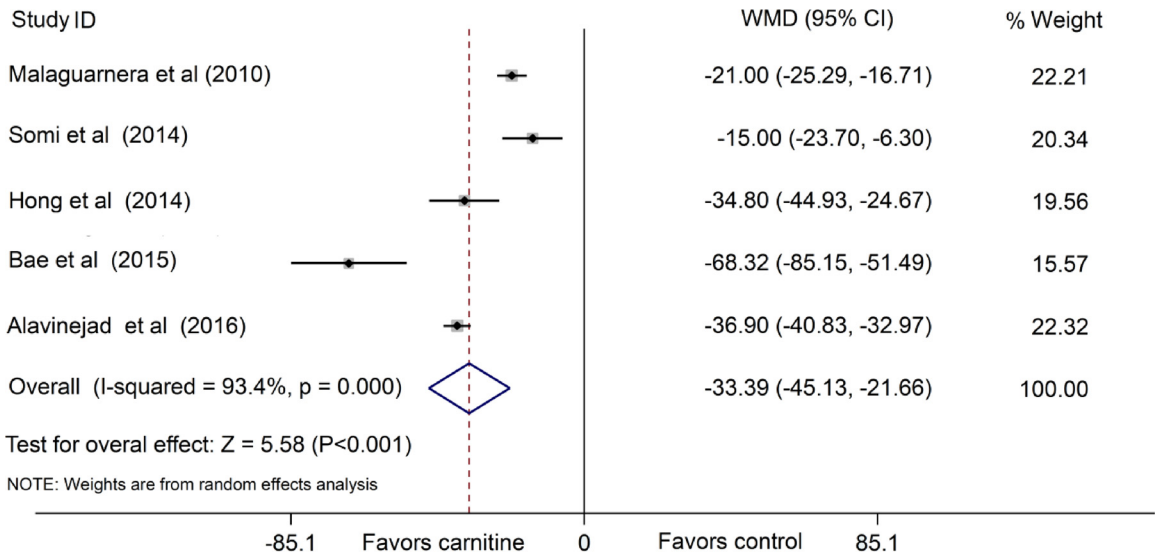

Fig. 3. Forest plot of ALT change outcome.

4.1. The effect of carnitine supplementation on liver function

In this study, we showed that carnitine supplementation significantly reduced AST, ALT, levels. However, no effects were seen on the γGT levels. In a meta-analysis conducted by Musso et al. (2010), L-carnitine supplementation improved liver function through a reduction in histological steatosis and NAS scores in NASH patients.[10] In another study, administration of 300 mg carnitine ortate for 12 weeks in patients with nonalcoholic fatty liver disease patients led to a remarkable reduction in the serum levels of total bilirubin and ALT.[12] Malaguarnera et al. (2010) in a randomised, double-blind, placebo-controlled study demonstrated that 2000 mg l- carnitine supplementation for 24 weeks could significantly reduce levels of AST, ALT, and γGT. However, no effects were seen on the albumin levels.[17] Serum levels of AST and ALT are usually used as biomarkers of liver damage.

However, in some patients with liver disease, these levels are within a normal range.[20,21] Damage of hepatic cells is a major factor which leads to the increase in the production and release of these enzymes.[22] Albumin is produced in the liver and reduced albumin production indicates liver dysfunction and would be considered as a risk factor for cirrhosis ascites.[23] On the other hand, Johnson et al. demonstrated that the serum albumin and bilirubin are beneficial in determining the severity of liver dysfunction.[24] Mitochondrial dysfunction causes overproduction of reactive oxygen species (ROS) and this consequently increases the peroxidation of the lipid membrane and overproduction of inflammatory factors, leading to the death of liver cells.[25,26]

A previous study demonstrated that carnitine could operate like a radical scavenger [27] by decreasing ROS production.[28] Furthermore, carnitine renders a protective effect by preventing the peroxidation of the lipid membrane and mitochondrial damage from the ROS effects.[29] In addition, carnitine reduces inflammatory responses through the transportation of long-chain fatty acid in the inner mitochondrial membrane and excretion of toxic substances from the metabolism of fatty acids.[30]

4.2. The effect of carnitine supplementation on lipid profile

The results of the current study demonstrated that carnitine supplementation significantly reduced TG levels. However, there were no effects on the total cholesterol, HDL-C, and LDL-C levels of nonalcoholic fatty liver disease patients. There is no meta-analysis as yet about the effects of carnitine supplementation on the lipid profile of nonalcoholic fatty liver disease patients. Huang et al. (2013) conducted a meta-analysis to assess the effects of L-carnitine supplementation on the serum lipid profile of haemodialysis patients. They demonstrated that L-carnitine supplementation did not have any effects on total cholesterol,

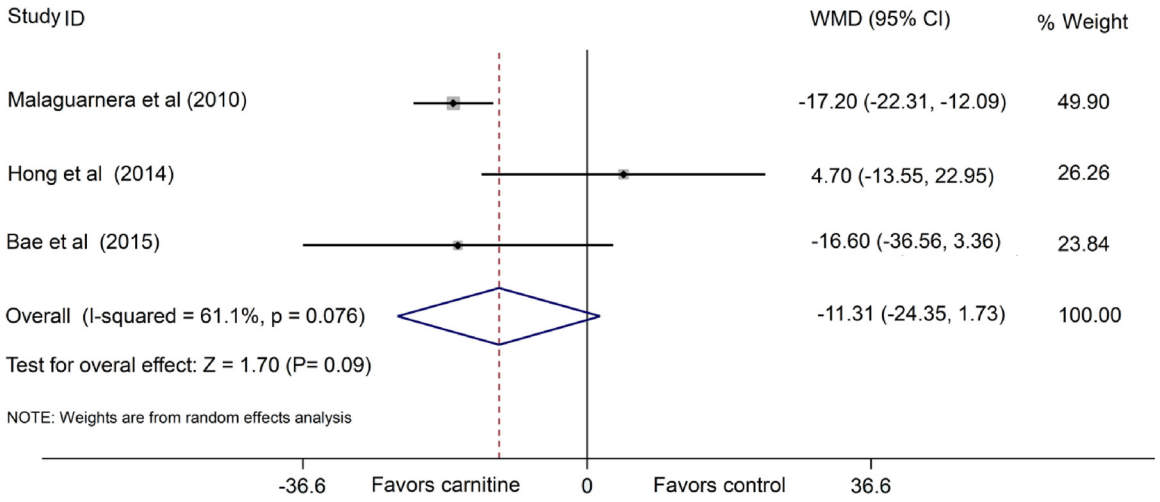

Fig. 4. Forest plot of γGT change outcome.

Table 3
The effects of carnitine supplementation on liver function tests (AST, ALT, and γ-GT), lipid profile (TG, TC, HDL-C, and LDL-C), BMI, body weight, and HOMA- IR in patients with nonalcoholic fatty liver disease based on subgroup analysis.

Variable	Subgroups		Number of effect sizes	WMD	(95 % CI)	P within group	P heterogeneity	I^2	P heterogeneity between sub-groups
AST	Trial duration (week)	> 3 months	2	−14.15	−36.78, 8.49	0.22	< 0.001	96.1 %	< 0.001
		≤ 3 months	3	−18.34	−35.55, −1.13	0.04	< 0.001	94.3 %	
	Participant's health status	NAFLD	4	−14.32	−28.95, 0.32	0.055	< 0.001	94.4 %	
		NASH	1	−25.60	−31.2, −20.00	< 0.001	< 0.001	–	
	Carnitine dose	> 500 mg	2	−26.55	−30.12, −22.97	< 0.001	0.67	0.0 %	
		≤ 500 mg	3	−9.18	−20.76, 2.40	0.12	0.002	83.4 %	
	Jaded score	> 3	3	−26.45	−29.87, −23.02	< 0.001	0.90	0.0 %	
		≤ 3	2	−2.70	−7.54, 2.13	0.27	0.93	0.0 %	
	Type of carnitine supplement	L-Carnitine	3	−18.64	−32.59, −4.68	0.01	< 0.001	94.5 %	
		Carnitine orotate Complex	2	−13.59	−35.59, 8.42	0.23	0.001	90.4 %	
ALT	Trial duration (week)	> 3 months	2	−19.24	−24.59, −13.89	< 0.001	0.23	32.0 %	< 0.001
		≤ 3 months	3	−44.37	−58.53, −30.21	< 0.001	0.001	84.8 %	
	Participant's health status	NAFLD	4	−37.26	−52.24, −22.29	< 0.001	< 0.001	91.7 %	
		NASH	1	−21.00	−25.29, −16.71	< 0.001	–	–	
	Carnitine dose	> 500 mg	2	−28.98	−44.56, −13.39	< 0.001	< 0.001	96.5 %	
		≤ 500 mg	3	−38.45	−64.61, −12.28	0.004	< 0.001	93.8 %	
	Jaded score	> 3	3	−39.54	−55.98, −23.11	< 0.001	< 0.001	95.9 %	
		≤ 3	2	−24.72	−44.12, −5.32	0.01	0.004	88.2 %	
	Type of carnitine supplement	L-Carnitine	3	−24.66	−37.69, −11.63	< 0.001	< 0.001	94.8 %	
		Carnitine orotate Complex	2	−50.86	−83.68, −18.04	0.002	0.001	91.1 %	
γ GT	Trial duration (week)	> 3 months	1	−17.20	−22.31, −12.09	< 0.001	–	–	0.08
		≤ 3 months	2	−5.55	−26.41, 15.31	0.60	0.12	58.0 %	
	Participant's health status	NAFLD	2	−5.55	−26.41, 15.31	0.60	0.12	58.0 %	
		NASH	1	−17.20	−22.31, −12.09	< 0.001	–	–	
	Carnitine dose	> 500 mg	1	−17.20	−22.31, −12.09	< 0.001	–	–	
		≤ 500 mg	2	−5.55	−26.41, 15.31	0.60	0.12	58.0 %	
	Jaded score	> 3	2	−17.16	−22.11, −12.22	< 0.001	0.95	0.0 %	
		≤ 3	1	4.70	−13.55, 26.95	0.61	–	–	
	Type of carnitine supplement	L-Carnitine	1	−17.20	−22.31, −12.09	< 0.001	–	–	
		Carnitine orotate Complex	2	−5.55	−26.41, 15.31	0.60	0.12	58.0 %	
TG	Trial duration (week)	> 3 months	1	−32.74	−55.45, −10.03	0.005	–	–	0.55
		≤ 3 months	3	−9.34	−34.26, 15.58	0.46	0.89	0.0 %	
	Participant's health status	NAFLD	3	−9.34	−34.27, 15.58	0.46	0.89	0.0 %	
		NASH	1	−32.74	−55.44, −10.03	0.005	–	–	
	Carnitine dose	> 500 mg	2	−21.81	−46.74, 3.13	0.09	0.18	44.5 %	
		≤ 500 mg	2	−14.59	−59.48, 30.30	0.52	0.69	0.0 %	
	Jaded score	> 3	3	−21.90	−40.13, −3.66	0.02	0.35	4.0 %	
		≤ 3	1	−21.50	−77.95, 34.95	0.45	–	–	
	Type of carnitine supplement	L-Carnitine	2	−21.81	−46.74, 3.13	0.09	0.18	44.5 %	
		Carnitine orotate Complex	2	−14.59	−59.48, 30.30	0.52	0.69	0.0 %	

(*continued on next page*)

Table 3 (*continued*)

Variable	Subgroups		Number of effect sizes	WMD	(95 % CI)	P within group	P heterogeneity	I^2	P heterogeneity between sub-groups
LDL-C	Trial duration	> 3 months	1	−44.85	−54.84, −34.86	< 0.001	–	–	< 0.001
	(week)	≤ 3 months	2	1.12	−5.80, 8.04	0.75	< 0.001	96.4 %	
	Participant's health status	NAFLD	2	1.12	−5.80, 8.04	0.75	< 0.001	96.4 %	
		NASH	1	−44.85	−54.84, −34.86	< 0.001	–	–	
	Jaded score	> 3	2	−20.80	−67.79, 26.19	0.39	< 0.001	98.1 %	
	Carnitine dose	≤3	1	−2.80	−14.74, 9.14	0.65	–	–	
		> 500 mg	1	−44.85	−54.84, −34.86	< 0.001	–	–	
		≤ 500 mg	2	1.12	−5.80, 8.04	0.75	< 0.001	96.4 %	
	Type of carnitine supplement	L-Carnitine	1	−44.85	−54.84, −34.86	< 0.001	–	–	
		Carnitine orotate Complex	2	1.12	−5.80, 8.04	0.75	< 0.001	96.4 %	
TC	Trial duration	> 3 months	1	−44.47	−54.77, −34.17	< 0.001	–	–	< 0.001
	(week)	≤ 3 months	2	1.17	−8.92, 11.25	0.82	0.40	0.0 %	
	Participant's health status	NAFLD	2	1.17	−8.92, 11.25	0.82	0.40	0.0 %	
		NASH	1	−44.47	−54.77, −34.17	< 0.001	–	–	
	Carnitine dose	> 500 mg	2	−19.20	−69.63, 31.23	0.46	< 0.001	96.1 %	
		≤ 500 mg	1	−2.00	−14.53, 10.53	0.75	–	–	
	Jaded score	> 3	2	−19.20	−69.63, 31.23	0.46	< 0.001	96.1 %	
		≤ 3	1	−2.00	−14.53, 10.53	0.75	–	–	
	Type of carnitine supplement	L-Carnitine	2	−19.20	−69.63, 31.23	0.46	< 0.001	96.1 %	
		Carnitine orotate Complex	1	−2.00	−14.53, 10.53	0.75	–	–	
HDL-C	Trial duration	> 3 months	1	3.10	1.61, 4.59	< 0.001	–	–	0.06
	(week)	≤ 3 months	2	0.08	−1.93, 2.08	0.94	0.86	0.0 %	
	Participant's health status	NAFLD	2	0.08	−1.93, 2.08	0.94	0.86	0.0 %	
		NASH	1	3.10	1.61, 4.59	< 0.001	–	–	
	Carnitine dose	> 500 mg	1	3.10	1.61, 4.59	< 0.001	–	–	
		≤ 500 mg	2	0.08	−1.93, 2.08	0.94	0.86	0.0 %	
	Jaded score	> 3	2	1.81	−1.01, 4.64	0.21	0.04	75.0 %	
		≤ 3	1	−0.20	−3.80, 3.40	0.91	–	–	
	Type of carnitine supplement	L-Carnitine	1	3.10	1.61, 4.59	< 0.001	–	–	
		Carnitine orotate Complex	2	0.08	−1.93, 2.08	0.94	0.86	0.0 %	
BMI	Trial duration	> 3 months	2	0.12	−0.12, 0.35	0.33	0.87	0.0 %	0.54
	(week)	≤ 3 months	2	−0.42	−1.15, 0.31	0.26	0.59	0.0 %	
	Participant's health status	NAFLD	3	0.08	−0.15, 0.30	0.50	0.38	0.0 %	
		NASH	1	−0.20	−1.28, 0.88	0.72	–	–	
	Carnitine dose	> 500 mg	1	−0.20	−1.28, 0.88	0.72	–	–	
		≤ 500 mg	3	0.08	−0.15, 0.30	0.50	0.38	0.0 %	
	Jaded score	> 3	2	0.10	−0.14, 0.33	0.42	0.58	0.0 %	
		≤ 3	2	−0.21	−0.99, 0.57	0.60	0.27	17.4 %	
	Type of carnitine supplement	L-Carnitine	2	−0.42	−1.15, 0.31	0.26	0.59	0.0 %	
		Carnitine orotate Complex	2	0.12	−0.12, 0.35	0.33	0.87	0.0 %	

(*continued on next page*)

Table 3 (*continued*)

Variable	Subgroups		Number of effect sizes	WMD	(95 % CI)	P within group	P heterogeneity	I^2	P heterogeneity between sub-groups
HOMA-IR	Trial duration (week)	> 3 months	1	−0.92	−1.12, −0.72	< 0.001	–	–	0.75
		≤ 3 months	2	−0.21	−2.11, 1.68	0.83	0.85	0.0 %	
	Participant's health status	NAFLD	2	−0.21	−2.11, 1.68	0.83	0.85	0.0 %	
		NASH	1	−0.92	−1.12, −0.72	< 0.001	–	–	
	Carnitine dose	> 500 mg	1	−0.92	−1.12, −0.72	< 0.001	–	–	
		≤ 500 mg	2	−0.21	−2.11, 1.68	0.83	0.85	0.0 %	
	Jaded score	> 3	2	−0.92	−1.11, −0.72	< 0.001	0.51	0.0 %	
		≤ 3	1	−0.40	−3.10, 2.30	0.77	–	–	
	Type of carnitine supplement	L-Carnitine	1	−0.92	−1.12, −0.72	< 0.001	–	–	
		Carnitine orotate Complex	2	−0.21	−2.11, 1.68	0.83	0.85	0.0 %	

AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; γGT, Gamma-glutamyltransferase; TG, triglycerides; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low- density lipoprotein cholesterol; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance.

HDL-cholesterol, and TG serum levels. Nevertheless, L-carnitine supplementation significantly reduced the LDL-cholesterol in haemodialysis patients.[31] In another meta-analysis, L-carnitine supplementation significantly decreased total cholesterol, LDL-C, HDL-C but did not have any effects on TG serum levels in adults with cardiovascular risk factors.[32]

Chen et al. (2014) showed in a meta-analysis that L-carnitine supplementation significantly reduced LDL-C. However, no significant effect was seen on the effect of L-carnitine on serum TG, cholesterol, and HDL levels in adults with end-stage kidney disease.[33] In a meta-analysis conducted by Vidal-Casariego et al. (2013), it was shown that L-carnitine supplementation could significantly reduce total cholesterol and LDL, but the changes in TG levels in this study were not significant for type 2 diabetes mellitus patients.[34] Furthermore, administration of carnitine ortate via carnitine-orotate complex 300 mg per day for 12 weeks to type 2 diabetes patients with NAFLD was not associated with any significant differences in TG, HDL-C, and LDL-C levels.[18]

The probable mechanism in which carnitine is able to affect lipid profile may be related to the beta-oxidation of fatty acids in muscle cells and hepatocytes, the reduction of the availability of free fatty acid which is used for TG synthesis, [35,36] and the decreased accumulation of short and medium-chain fatty acids in mitochondria.[37] In contract, carnitine palmitoyltransferase (Cpt) is a fundamental enzyme in the oxidation of fatty acid that is activated by carnitine.[9] Furthermore, previous studies have shown that TG had a strong significant relationship with NAFLD. Therefore, TG is one of the NAFLD markers.[38] Under conditions such as over-nutrition, insulin resistance, and carbohydrate-rich diets, the balance of the TG storage in the liver is disrupted and this may cause excessive accumulation in hepatocytes.[39–41] L-carnitine has been proven to be able to reduce TG, thus supplementation with L-carnitine can improve liver function and prevent excess TG accumulation in hepatocytes and hepatic steatosis.

L-carnitine can affect liver function via its effect on Insulin Resistance (IR). Results from previous studies have shown that IR and TG are significantly correlated in which decreasing IR reduces TG levels.[42] Since IR exists in many diseases and has a significant correlation with TG levels, supplementation with L-carnitine in the IR treatment reduces TG levels significantly and thus prevents its accumulation in hepatocytes. On the other hand, IR affects many intracellular pathways of substrate disposition in the liver and peripheral tissues.[43] The peripheral IR may contribute to the development of hepatic steatosis due to excess NEFA (Non-Esterified Fatty Acid) flux.[44] As a result, L-carnitine supplementation by IR treatment improves the function of intracellular pathways and reduces NEFA flux.

4.3. The effect of carnitine supplementation on BMI, body weight, and HOMA-IR

The present study shows that carnitine supplementation significantly reduced HOMA-IR. However, no effects were seen on BMI and body weight. Homeostasis model assessment of Insulin Resistance (HOMA-IR) has been extensively used in the clinical assessment of insulin sensitivity. A higher score of HOMA-IR represents more severe insulin resistance (IR).[45] Therefore, a meta-analysis was conducted to evaluate the effect of L-carnitine on HOMA-IR. Gholipur-Shahraki et al. (2109) in a meta-analysis in patients with chronic kidney disease showed that there were no conclusive effects of carnitine on body weight and BMI.[46] However, Pooyandjoo et al. (2016) in a meta-analysis demonstrated that L- carnitine supplementation could significantly reduce body weight and body mass index.[47]

In a meta-analysis, Fathizadeh et al., (2019) showed that L-carnitine supplementation significantly reduced fasting plasma glucose (FPG), insulin, HOMA-IR [48] According to a meta-analysis by Ying Xu et al. (2017), supplementation with L-carnitine was beneficial in the treatment of IR. The longer the duration of the supplementation, the more evident the therapeutic effect would be.[49] Differences between results

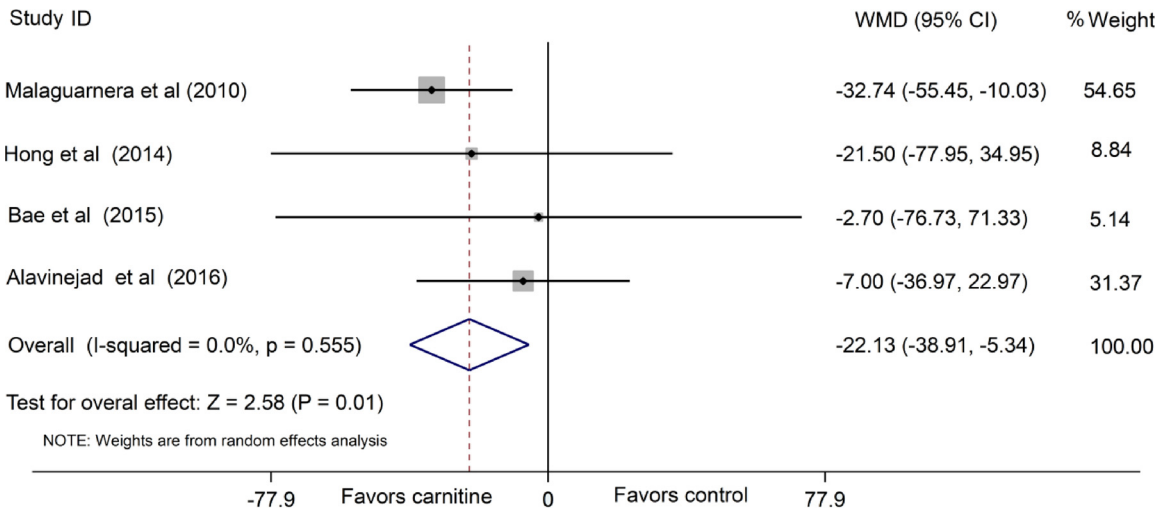

Fig. 5. Forest plot of TG change outcome.

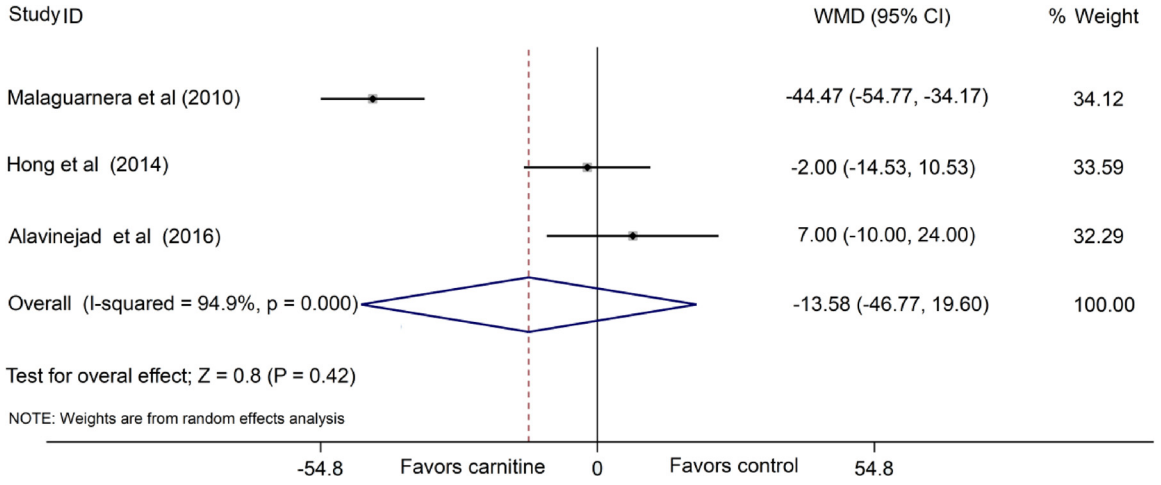

Fig. 6. Forest plot of cholesterol change outcome.

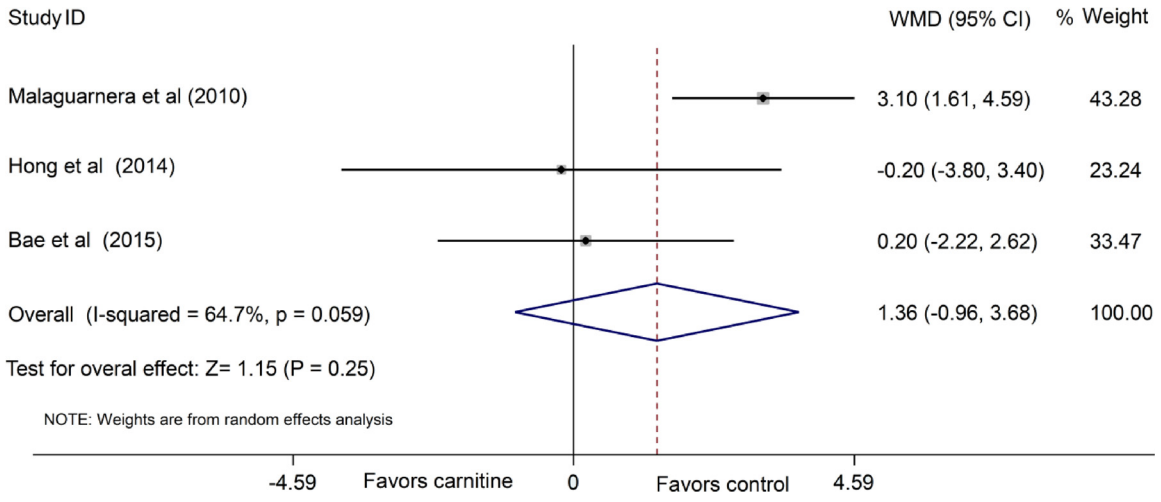

Fig. 7. Forest plot of HDL-C change outcome.

can be due to study design, duration of the study, the dosage of carnitine supplementation, participants' health status, and types of carnitine supplement. The probable mechanism for beneficial effect of carnitine supplementation on IR may be related to changing gene expression involved in insulin signaling pathway, decreasing the expression of glycolytic and gluconeogenic enzymes, and modulating the ratio of the intra-mitochondrial acyl-CoA/CoA and the pyruvate dehydrogenase complex activity [50]

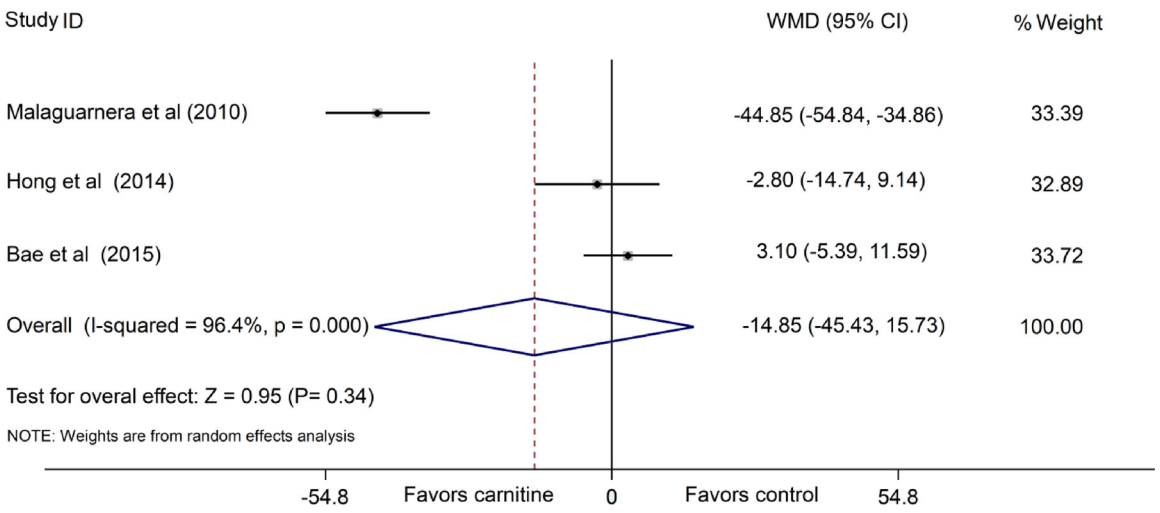

Fig. 8. Forest plot of LDL-C change outcome.

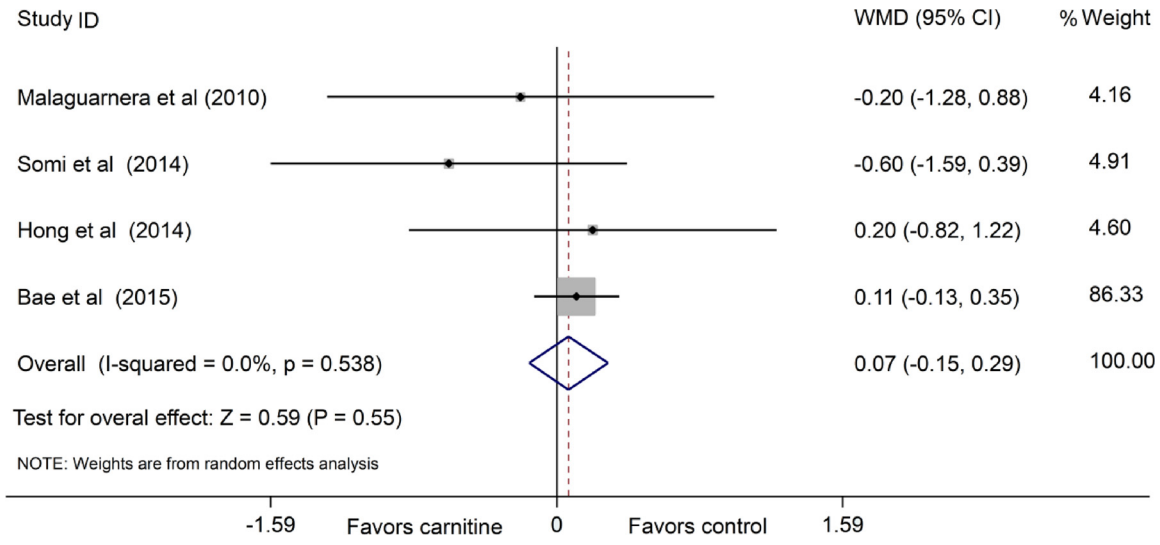

Fig. 9. Forest plot of BMI change outcome.

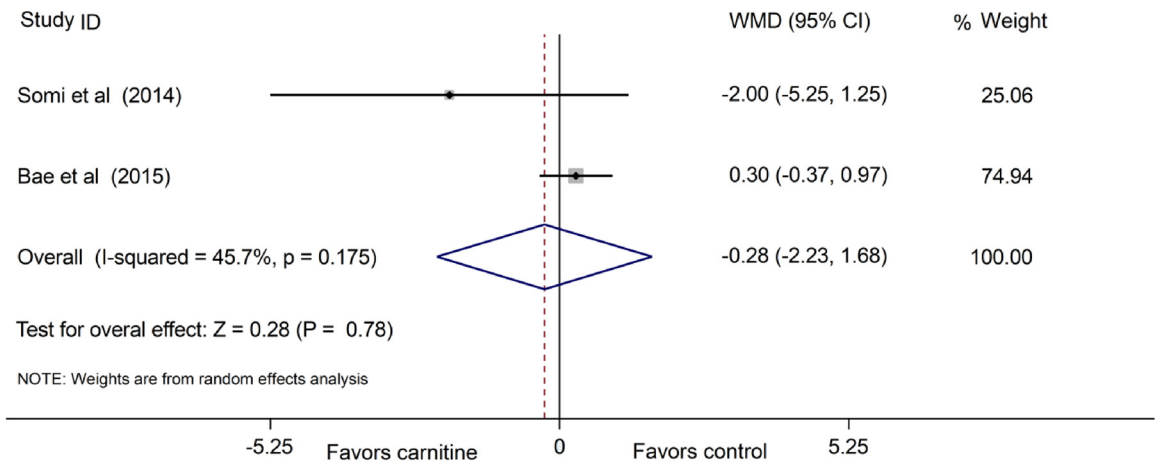

Fig. 10. Forest plot of body weight change outcome.

4.4. Strengths and weaknesses of the study

This meta-analysis has several strengths. First, to make up for the fact that the results showed no heterogeneity between some of the studies included in the final analysis, we performed a sub-group analysis for all the biomarkers based on trial duration, participants' health status, carnitine dose, Jaded score, and type of carnitine supplement. Secondly, the duration of the studies varied from 12 weeks to 24 weeks.

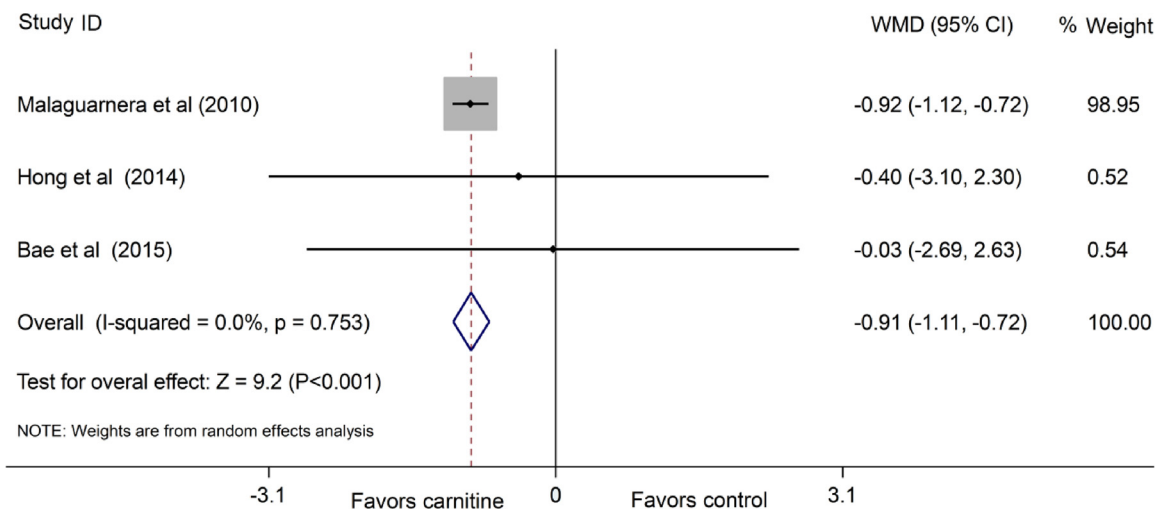

Fig. 11. Forest plot of HOMA-IR change outcome.

Table 4
The results of the pooled effect size by leave-one-out sensitivity analysis.

Variable	Pre-sensitivity analysis			Upper & lower of effect size	Post-sensitivity analysis		
	Number of effect sizes	Pooled WMD (random effect)	95 % CI		Pooled WMD (random effect)	95 % CI	Excluded studies
AST	5	−16.62	−28.11, −5.14	Upper	−13.82	−27.27, −0.37	Alavinejad et al
				Lower	−20.19	−31.72, −8.66	Somi et al
ALT	5	−33.39	−45.13, −21.66	Upper	−26.97	−37.72, −16.22	Bae et al
				Lower	−38.07	−51.13, −25.01	Somi et al
γGT	3	−11.31	−24.35, 1.73	Upper	−5.55	−26.41, 15.31	Malaguarnera et al
				Lower	−17.16	−22.11, −12.22	Hong et al
TG	4	−22.13	−38.91, −5.34	Upper	−9.34	−34.26, 15.59	Malaguarnera et al
				Lower	−29.04	−49.30, −8.78	Alavinejad et al
TC	3	−13.58	−46.77, 19.60	Upper	1.16	−8.92, 11.25	Malaguarnera et al
				Lower	−23.39	−65.01, 18.23	Alavinejad et al
HDL-C	3	1.36	−0.96, 3.68	Upper	1.87	−1.25, 5.00	Bae et al
				Lower	0.08	−1.93, 2.08	Malaguarnera et al
LDL-C	3	−14.85	−45.43, 15.73	Upper	1.12	−5.80, 8.04	Malaguarnera et al
				Lower	−23.96	−65.16, 17.25	Bae et al
BMI	4	0.07	−0.15, 0.29	Upper	0.10	−0.12, 0.33	Somi et al
				Lower	−0.21	−0.80, 0.38	Bae et al
Body weight	2	−0.28	−2.23, 1.68	Upper	0.30	−0.37, 0.97	Somi et al
				Lower	−2	−5.25, 1.25	Bae et al
HOMA-IR	3	−0.91	−1.11, −0.72	Upper	−0.21	−2.11, 1.68	Malaguarnera et al
				Lower	−0.97	−1.11, −0.72	Bae et al

AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; γGT, Gamma-glutamyltransferase; TG, triglycerides; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low- density lipoprotein cholesterol; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance.

This variation was able to demonstrate the moderate and long-term impacts of L-carnitine on liver function, lipid profile, BMI, body weight, and HOMA-IR of nonalcoholic fatty liver disease patients. Thirdly, there were no studies with a high risk of bias. Fourthly, we utilised a random effect model for meta-analysis which allows us to determine any heterogeneity among the studies.

However, there are also certain limitations to this study. Firstly, the final quantitative analysis of data was based on the low number of RCTs because of the limited studies available in this area. Secondly, the total sample size was small and included only 334 patients. This may not be representative of all the patient population. Thirdly, due to the limited number of studies available in this field, low-quality studies with poor Jaded score were included for data analysis and could not assess the effects of carnitine supplementation on albumin and bilirubin levels in this meta-analysis. Finally, baseline carnitine deficiency and different dosages of carnitine supplementation were not evaluated among the studies.

5. Conclusions

Overally, the findings of this study demonstrated that carnitine supplementation decreased AST, ALT, TG levels and HOMA-IR. Nevertheless, it did not affect γGT, LDL-C, HDL-C levels, BMI and body weigh in patients with non-alcoholic fatty liver. To confirm the effect of carnitine supplementation on nonalcoholic fatty liver disease patients, more well-established prospective studies need to be conducted in the future.

Author contributions

Design and systematically search for articles have been done by AM and MZ. Articles review, selection, and data extraction conducted by ZH, AM. Analysis of data and manuscript writing were performed by AM, S.MR, and LM. All procedure has been accomplished under supervision BN.

Declaration of Competing Interest

No conflict of interest declared by the authors.

Funding

This study was funded by a grant from Universiti Putra Malaysia Number FRGS 2018-1 (ID 218776).

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