The Role of L-Carnitine in the Improvement of Liver Tests and Glycemic Control among Patients with Non-Alcoholic Fatty Liver Disease: A Meta-Analysis

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Abstract

Background: Population-based cohort studies from Asia have reported rising prevalence of non-alcoholic fatty liver disease (NAFLD) from 10% to 24%. Philippine data report a rate of 12.2% with important co-morbidities such as obesity (56%) and diabetes mellitus (69%). Several interventions for NAFLD have emerged, among which L-carnitine has shown promise. *Objective:* This meta-analysis aimed to assess the role of carnitine in improving liver function and glycemic control among NAFLD patients. *Methodology:* Electronic search from databases (PubMed, Cochrane Library and Google Scholar) yielded five randomized controlled trials. Studies included adult patients with NAFLD diagnosed through clinical and/or histologic findings. Methodologic assessment of studies and statistical analyses were performed with Review Manager version 5.3. *Results:* Of 33 studies identified, five fulfilled the inclusion criteria with a total of 340 clinical subjects. Pooled analysis showed significant reduction in serum ALT and AST with mean differences of 34.64 $\pm$ 14.3 (p value = <0.0001) and 17.49 $\pm$ 9.88 (p value = 0.0005), respectively. No significant reduction on BMI and fasting blood sugar were demonstrated with mean differences of -0.10 $\pm$ 0.20 (p value = 0.31) and 2.31 $\pm$ 13.38 (p value = 0.73), respectively. Subgroup analysis based on treatment dose and duration showed unaltered results except for AST levels, which demonstrated greater reduction at carnitine dose of >500 mg/day. *Conclusion:* The use of L-carnitine resulted in lower ALT and AST levels, with dose-dependent reduction seen for AST. Intake of L-carnitine had no effect on glycemic control and BMI among NAFLD patients. Further studies involving more clinical subjects with histologic and radiologic assessments as outcomes are highly recommended.

Keywords: carnitine, carnitine-orotate, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, meta-analysis

Introduction

The prevalence of non-alcoholic fatty liver disease (NAFLD) is rising in concert with rising rates of obesity and diabetes mellitus, with an estimated 33.8% and 10.6% of the population meeting the criteria, respectively. Subsequent population-based cohort studies from China, Japan, and Korea have reported a prevalence of NAFLD ranging from 10% to 24% using ultrasonography.[1] Furthermore, this prevalence resembles our local statistics as evidenced by a cohort study published in 2008 stating a 12.2% rate of NAFLD based on clinical and ultrasonographic findings.[2] The study also emphasized an increased rate of obesity (56%) and diabetes (69%) across all of these populations. This emerging clinical condition holds a relevant impact since it is associated with various important co-morbidities that highly contribute to the burden of the disease, including diabetes mellitus, obesity and dyslipidemia.

Several mechanisms have been implicated in the development of NAFLD across its spectrum, ranging from steatosis to eventual liver cirrhosis. The popular "two-hit" hypothesis by which sequential progression

from isolated fatty liver (IFL) to non-alcoholic steatohepatitis (NASH) involves an initial lesion of hepatic steatosis followed by a second "hit" of oxidative stress resulting in liver injury.[3] Another etiology that greatly contributes to this process is insulin resistance, which has been associated with NAFLD. This metabolic state results in several changes in lipid metabolism including enhanced peripheral lipolysis, increased triglyceride synthesis and increased hepatic uptake of fatty acids. It is now recognized that patients who have steatohepatitis on liver biopsy specimens are at risk of progression to cirrhosis, and our understanding of the pathogenesis of NAFLD has evolved from the initial two-hit hypothesis concept to the introduction of emerging therapeutic interventions, including ursodeoxycholic acid, vitamin E and carnitine, to manage such disease condition.[4]

L-carnitine is a quaternary amine, which has been hypothesized to improve the outcome of NASH, because it reduces lipid levels, limits oxidative stress, and modulates inflammatory responses.[5] It performs a number of essential intracellular and metabolic functions, such as fatty acid transport between cytosol and mitochondria, detoxification of potentially toxic metabolites, regulation of the mitochondrial acyl-Co A/CoA ratio, and stabilization of cell membranes. Many studies have found that treatment with such drug has a substantial role in glucose tolerance, weight loss, fatty acid metabolism and insulin function.[6] Multiple randomized controlled trials have been published stating the beneficial effects of the use of L-carnitine in improving liver tests and glycemic control among patients with NAFLD.

The aim of this study is to synthesize data from pooled randomized controlled trials involving this emerging intervention, and to address the question of how effective the use of L-carnitine is in the improvement of liver tests and glycemic control among patients with NAFLD. The general objective of this research is to determine the efficacy of L-carnitine in the improvement of liver tests and glycemic control among patients with NAFLD. The following are the specific objectives: (1) To determine improvement in liver enzymes including AST, ALT among patients treated with L-carnitine versus the control group; (2) To determine improvement in glycemic control through serial fasting blood sugar (FBS) monitoring among NAFLD patients treated with L-carnitine versus the control group; (3) To determine the effects of L-carnitine on other anthropometric profiles including body mass index (BMI); and (4) To determine any possible adverse effects related to L-carnitine among patients with NALFD, if available.

Methodology

Database and Search Strategy

Electronic databases including PubMed, Cochrane Library and Google Scholar were used to retrieve articles from January 1986 (when the drug was approved by the US FDA for public use) up to November 2019. The following were the search terms/keywords used: L-carnitine, carnitine, carnitine-orotate, NASH, non-alcoholic steatohepatitis, NAFLD, and non-alcoholic fatty liver disease. No language and publication restrictions were used during the search of articles. We also obtained primary sources from hand searches with references encountered upon review of papers and original articles. Only original data were used in the meta-analysis.

Eligibility Criteria

The articles were considered eligible if the studies met the following criteria: randomized controlled trials (RCT) conducted among adult patients $\geq$18 years of age with NAFLD; use of either oral or intravenous L-carnitine or carnitine-orotate complex as the intervention compared to placebo or standard-of-care treatment (i.e., metformin for diabetes mellitus) with outcomes being change in the serum levels of liver enzymes, FBS, BMI, and other metabolic profiles if available. Studies which were non-RCTs (including retrospective studies and case reports or reviews) were excluded. Subsequently, patients known to have alcoholic fatty liver disease and significant alcohol consumption (20 gm/day for males and 10 gm/day for females), and hepatocellular carcinoma or cirrhosis related to other etiologies were excluded.

Selection of Studies

The study included trials discussing treatment effects of L-carnitine or L-carnitine orotate complex in the improvement of liver function and metabolic profile, including BMI and glycemic control, among patients with NAFLD. Three independent reviewers thoroughly assessed and identified available trials by

applying the inclusion and exclusion criteria mentioned above. Any disagreement in article inclusion and data extraction was solved by discussion and proper adjudication by the consultant co-author who stood as the fourth reviewer.

A comprehensive literature search was performed and we were able to identify 33 references from various electronic databases including the following: 18 from PubMed, nine from the Cochrane Library, and six from Google Scholar. Three additional articles were retrieved through hand search. Out of the 33 articles, six studies were fully reviewed and assessed for eligibility. One study was excluded due to its use of a different intervention in the placebo arm and the use of median as a measure among serial laboratory determinations. An effort to reach the investigators was made to obtain raw data for laboratory values but to no avail. Hence, this resulted in the analysis of five RCTs (see **Figure 1**).

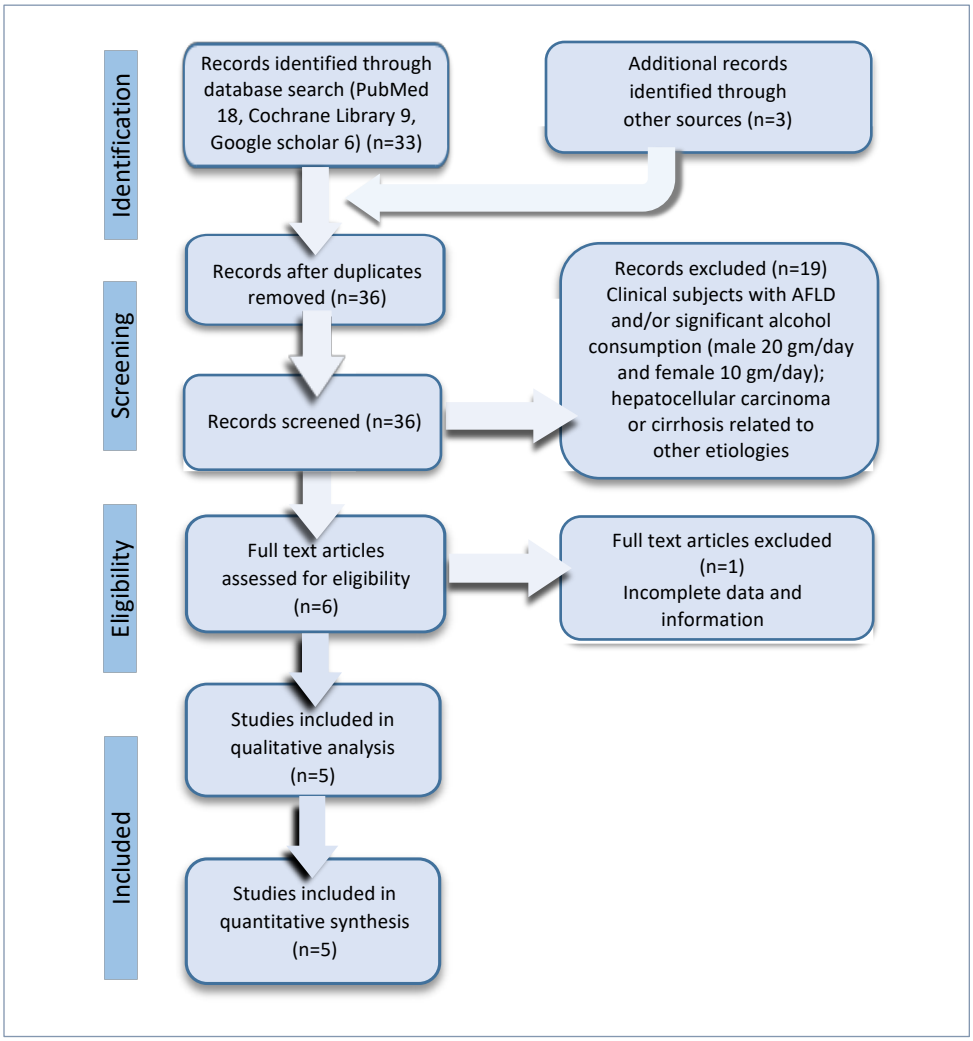


Figure 1. Flow diagram of the study selection

Quality Assessment of Selected Studies

The quality of included trials was duly assessed using the Cochrane Collaboration Risk of Bias Tool available in the Review Manager version 5.3 software. Domains including method of randomization, allocation concealment, blinding, follow-up rate and reporting bias were taken into account. They were evaluated by the investigators and classified as low, high or unclear

risk of bias. The qualities of the five randomized studies are summarized in **Figure 2**. Overall, there was essentially low risk of bias for most of the domains except for the method of allocation concealment which was not stated in the majority of the RCTs included.

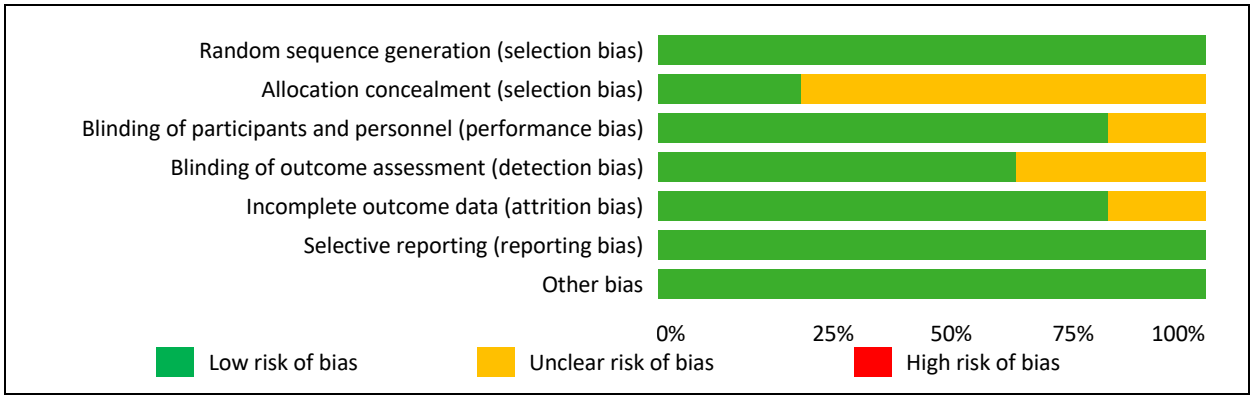


Figure 2. Risk of bias graph of included randomized controlled trials

Statistical Analysis

All statistical analyses were performed using Review Manager 5.3. Heterogeneity was assessed using the Chi-square statistic and a *p* value of less than 0.05 was considered to represent statistical significance. The degree of heterogeneity was determined by the I^2 value.

Additionally, sensitivity analyses were conducted to determine the stability of the overall effects by dividing the studies based on both treatment dose and treatment duration.

Results

Characteristics of Included Studies

The characteristics of the included studies that assessed the efficacy of L-carnitine or carnitine-orotate complex in the improvement of liver tests and glycemic control are shown in **Table 1**. Five studies presented results on improving liver tests as well as other metabolic parameters as outcomes, including glycemic control and BMI. Various doses and different dosing frequencies of L-carnitine or carnitine-orotate were used in the study ranging from 300 mg/day to 2,342 mg/day. Majority of the studies had treatment duration of 90 days, except for two studies extending up to 24 weeks or 180 days.

Table 1. Basic characteristics of included studies

	RCT1 Malaguarnera et al.[7]		RCT2 Hong et al.[8]		RCT3 Bae et al.[9]		RCT4 Alavinejad et al.[10]		RCT5 Somi et al.[11]	
	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control
No. of participants	36	38	24	24	39	39	30	30	40	40
Country	Italy	Italy	Korea	Korea	Korea	Korea	Iran	Iran	Iran	Iran
Ave. Age (yrs)	47.9	47.8	51.5	52	51	52	60	59	40.3	41
Male (%)	53	56	69	69	64	74	78	65	83	83
Female (%)	47	34	31	31	36	24	22	35	17	17
BMI (kg/m^2)	26.5	26.5	27.2	27	28.2	26.7	28.6	29.5	29.4	28.6
FBS (mg/dL)	110.5	109.8	141	147.8	143.6	153.4	172	175	NS	NS
ALT (IU/L)	120.2	125.7	71.2	67.1	94.9	79.2	124	120	81.7	54.1
AST (U/L)	135.4	132.8	44.3	44.4	61.8	51.7	122.7	125.3	60.5	52.6

Treatment dosage	L-carnitine 2000 mg/day		Carnitine-orotate complex 300 mg/day (2 tabs TID)		Carnitine-orotate complex 2472 mg/day (824 mg TID)		L-carnitine 750 mg/day		L-carnitine 500 mg/day	
Outcomes measured	ALT, ɣ-GTP, albumin, lipid profile, insulin, C peptide, CRP, ALP		Primary: ALT; Secondary: FBS, Hba1c, AST, mtDNA, 8-hydroxydeoxyguanine		Primary: decline in ALT to normal range; Secondary: hepatic steatosis using HU via non-contrast CT, AST, FBS, HBa1c, HOMA-IR, HOMA-B, TG, LDL, HDL, weight, BMI		AST, ALT, TC, TG, FBS, Hba1c		Weight, BMI, AST, ALT	
Country	Italy		Korea		Korea		Iran		Iran	
No. of participants	36	38	24	24	39	39	30	30	40	40

Abbreviations: AST - aspartate aminotransferase; ALT – alanine aminotransferase; FBS – fasting blood sugar; BMI – body mass index; ɣ-GTP – gamma glutanyl transpeptidase; HOMA IR – homeostatic model assessment for insulin resistance; TC - total cholesterol; TG – total glyceride; LDL – low density lipoprotein mtDNA – mitochondrial DNA; CRP – C-reactive protein

The age of participants in each trial ranged from 40 to 60 years old. The total number of pooled subjects from the clinical trials summed up to 340 patients with 169 (49.7%) and 171 (50.3%) for the treatment and control groups, respectively. There were 234 (68.82%) male subjects and 106 (31.2%) female participants. Of note was the prevalence of an overweight BMI across all studies. The RCTs were generally conducted in Asian countries, including Iran and Korea, except for one study which was done in Italy.

Primary Outcomes

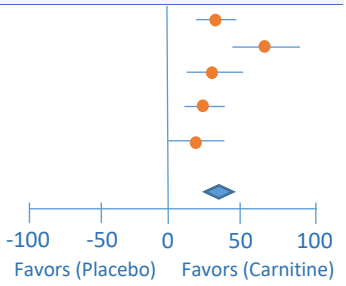
Change in Serum ALT Levels

Pooled analysis using random effects model of the five trials evaluating the role of L-carnitine or carnitine-orotate complex supplementation in the change of serum ALT levels showed a significant reduction with a mean difference of 34.64 (95% CI 20.34-48.94) and a *p* value of <0.00001. Significant heterogeneity was present with an I^2 of 87% (see **Table 2**).

Table 2. Forest plot on the change of serum ALT from baseline between treatment (carnitine) and control group

Study or Subgroup	Carnitine			Placebo			Weight (%)	Mean Difference IV, random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Alavinejad, 2016	41.9	12.43	30	5.0	12.45	30	23.3	36.90[30.60, 43.20]
Bae, 2015	73.7	38.7	39	5.38	37.1	39	18.2	68.32 [51.49, 85.15]
Hong, 2014	51.5	33.2	24	16.7	31.3	24	17.5	34.80 [16.55, 53.05]
Malaguarnera, 2009	58.4	22.6	36	37.4	12.1	38	22.5	21.00 [12.68, 29.32]
Somi, 2014	30.7	46.48	40	15.7	25.8	40	18.4	15.00 [-1.47, 31.47]
Total (95% CI)			**169**			**171**	**100**	**34.64 [20.34, 48.94]**

Heterogeneity: Tau^2 = 218.01; Chi^2 = 31.00, df = 4 (P <0.00001); I^2 = 87%
Test for overall effect: Z = 4.75 (P <0.00001)



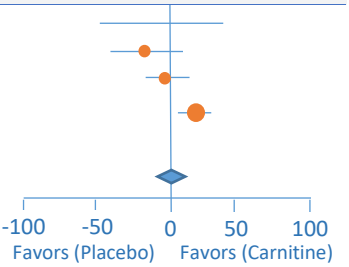
Change in Serum FBS Level

Four studies were included in the group analysis evaluating the effect of L-carnitine/carnitine-orotate in the glycemic control among patients with NAFLD. The test showed no significant difference between the experimental and the control group with a weighted mean difference of 2.31 (95% CI 11.6-15.69) and a *p* value of 0.73. The I^2 was 57% which represents moderate heterogeneity (see **Table 3**).

Table 3. Forest plot on the change of fasting blood sugar from baseline between treatment (carnitine) and control group

Study or Subgroup	Carnitine			Placebo			Weight	Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	(%)	IV, random, 95% CI	IV, random, 95% CI
Alavinejad, 2016	7	83.63	30	6	85	30	8.2	1.00[-41.67, 43.67]	
Bae, 2015	2.2	34.5	39	16.9	65.2	39	19.8	-14.70 [-37.85, 8.45]	
Hong, 2014	16.4	28	24	17.6	24.6	24	30.2	-1.20 [-16.11, 13.71]	
Malaguarnera, 2009	14.4	15.88	36	1.26	17.45	38	41.9	13.14 [5.54, 20.74]	
Total (95% CI)			**129**			**131**	**100**	**2.31 [-11.06, 15.69]**	

Heterogeneity: Tau^2 = 96.27; Chi^2 = 7.02, df = 3 (P = 0.07); I^2 = 57%
Test for overall effect: Z = 0.34 (P = 0.73)



Secondary Outcomes

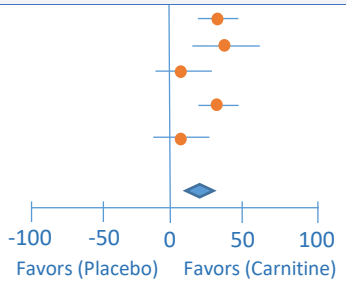
Change in Serum AST Levels

Grouped analysis of included trials evaluating change in serum AST levels among patients in the experimental group showed significant decrease from the baseline compared to placebo with a weighted mean difference of 17.49 (95% CI 7.61-27.36) and a *p* value of 0.003. There was substantial heterogeneity among the studies with an I^2 of 75% (see **Table 4**).

Table 4. Forest plot on the change of AST from baseline between treatment (carnitine) and control group

Study or Subgroup	Carnitine			Placebo			Weight	Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	(%)	IV, random, 95% CI	IV, random, 95% CI
Alavinejad, 2016	26.4	15. 3	30	0.8	11	30	25.60	25.60[18.86, 32.34]	
Bae, 2015	26.1	22.9	39	0.72	30.1	39	19.7	25.38 [13.51, 37.25]	
Hong, 2014	10.5	25.6	24	7.6	20.8	24	18.5	2.90 [-10.30, 16.10]	
Malaguarnera, 2009	71.7	22.9	36	46.1	24.94	38	20.6	25.60 [14.70, 36.50]	
Somi, 2014	15.6	36.34	40	13.1	32.26	40	16.8	2.50 [-12.56, 17.56]	
Total (95% CI)			**169**			**171**	**100**	**17.49 [7.61, 27.36]**	

Heterogeneity: Tau^2 = 92.26; Chi^2 = 16.00, df = 4 (P = 0.003); I^2 = 75%
Test for overall effect: Z = 3.47 (P = 0.0005)



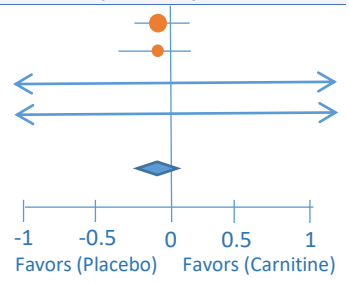
Change in Body Mass Index

Of the five studies, there were four RCTs that evaluated the use of L-carnitine in the improvement of anthropometric measurement including BMI, which is known to highly correlate with insulin resistance and NAFLD. In this analysis, no significant reduction was seen as noted by the mean difference of -0.10 (95% CI 0.30-0.10) and a *p* value of 0.31. The studies were deemed homogeneous with a Chi-square value of 0.40 and I^{2}of 0% (see **Table 5**).

Table 5. Forest plot on the change of BMI from baseline between treatment (carnitine) and control group

Study or Subgroup	Carnitine			Placebo			Weight	Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	(%)	IV, random, 95% CI	IV, random, 95% CI
Bae, 2015	0.14	0.58	39	0.25	0.25	39	69.9	-0.11[-0.35, 0.13]	
Hong, 2014	0.3	0.6	24	0.4	0.4	24	28.7	--0.10 [-0.47, 0.27]	
Malaguarnera, 2009	1.1	5.4	38	1.3	1.3	36	0.7	--0.20 [-2.59, 2.19]	
Somi, 2014	0.8	5.586	40	0.2	0.2	40	0.8	0.60 [-1.61, 2.81]	
Total (95% CI)			**141**			**139**	**100**	**-0.10 [-0.30, 0.10]**	

Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.40, df = 3 (P = 0.94); I^2 = 0%
Test for overall effect: Z = 1.01 (P = 0.31)



Subgroup Analysis

A subgroup analysis was performed to assess whether results varied by the treatment dosage and duration of the intervention. We divided subgroups into treatment dosage comparing doses of the intervention between ≤500 mg/day and >500 mg/day. Treatment durations were divided into 90 and 180 days accordingly.

Change in Serum ALT Levels

The pooled analysis revealed that the significant reduction in ALT remained unaltered regardless of the treatment dose and duration. Between doses of >500 mg/day and ≤500 mg/day, ALT remained significantly reduced at a mean difference of 48.21 (*p* value 0.0001) and 24.49 (*p* value 0.01), respectively. In comparing subgroups based on treatment duration, improvement in serum ALT was still achieved with a weighted mean difference of 19.78 (*p* value of <0.00001) in 180 days. However, this was grossly less compared to the pooled analysis of three studies with treatment duration of 90 days with a weighted mean difference of 46.05 (*p* value of <0.00001) (see **Table 6**.)

Table 6. Subgroup analysis comparing the effects of L-carnitine on serum ALT level based on treatment dose and duration

	No. of Studies	Weighted Mean Difference (95% CI)	*p* value within group	*p* value of heterogeneity	I^2
Treatment Dose					
>500 mg/day	3	48.21 (29.96, 66.46)	0.00001	0.003	0.83
≤500 mg/day	2	24.49 (5.11, 43.88)	0.01	0.11	0.60
Treatment Duration					
90 days	3	46.05 (26.73, 65.36)	<0.00001	0.002	0.84
180 days	2	19.78 (12.35, 27.21)	<0.00001	0.52	0.00

Change in Serum FBS Level

The subgroup analysis revealed no significant FBS reduction across all treatment doses and durations except for the treatment duration of 180 days. However, this comparison was only demonstrated by one trial[7] (see **Table 7**).

Table 7. Subgroup analysis comparing the effects of L-carnitine on serum FBS level based on treatment dose and duration

	No. of Studies	Weighted Mean Difference (95% CI)	*p* value within group	*p* value of heterogeneity	I^2
Treatment Dose					
>500 mg/day	3	2.21 (-18.05, 22.47)	0.83	0.07	0.62
≤500 mg/day	1	-1.2 (-16.11, 13.71)	0.87	N/A	N/A
Treatment Duration					
90 days	3	-4.67 (-16.7, 7.36)	0.45	0.61	0.0
180 days	1	13.14 (5.55, 20.74)	0.0007	N/A	N/A

Change in Serum AST Level

In this analysis, AST was proven to be more significantly reduced with the use of L-carnitine at a dosage of >500 mg/day, having a weighted mean difference of 25.56 (20.39, 30.72) and a *p* value of <0.00001, compared to the use of carnitine at ≤500 mg/day (WMD: 2.73 (-7.20, 12.65), *p* value of 0.59. Furthermore, the use of L-carnitine for 90 days showed greater reduction in AST than treatment for 180 days. (see **Table 8**).

Table 8. Subgroup analysis comparing the effects of L-carnitine on serum AST level based on treatment dose and duration

	No. of Studies	Weighted Mean Difference (95% CI)	*p* value within group	*p* value of heterogeneity	I^2
Treatment Dose					
>500 mg/day	3	25.56 (20.39, 30.72)	<0.00001	1.0	0.0
≤500 mg/day	2	2.73 (-7.20, 12.65)	0.59	0.97	0.0
Treatment Duration					
90 days	3	18.75 (5.64, 31.86)	0.005	0.009	0.79
180 days	2	14.6 (-7.95, 37.26)	0.20	0.01	0.83

Safety

Of the five studies included in the analysis, not one study measured or evaluated safety or adverse events as an outcome of interest.

Discussion

Apart from diet and lifestyle modification, various pharmacologic interventions have already emerged and studied to assess their use in the management of non-alcoholic fatty liver disease. In this meta-analysis, we were able to present the effects of L-carnitine in several surrogate markers of liver integrity, including AST, ALT and other metabolic profiles including glycemic control (fasting blood sugar) and anthropometric index (BMI) among patients with NAFLD. Previous systematic reviews done by Rad et al.[12] and Abolfathi et al.[13] included different subgroups of patients including subjects with pure cardiac, thyroid or other liver disorders. Among the studies mentioned, no analysis has been performed to evaluate the effects of L-carnitine on glycemic control, i.e., serum fasting blood sugar. To the best of our knowledge, this is the first meta-analysis that assessed the clinical characteristics mentioned.

The synthesis of data pooled from several RCTs confirmed the beneficial effects of L-carnitine in the improvement of liver function based on the serum markers measured (AST, ALT). Furthermore, the subgroup analysis was able to emphasize its consistent use across all treatment doses and duration except for the reduction of AST which is better achieved with a dose of >500 mg/day. The oral supplementation of L-carnitine (1-6 gm) has been reported to only have a biological availability of from 5% to 18%. This limited bioavailability is associated with the metabolization of L-carnitine by gut microbiota prior to absorption.[14] Hence, this unique pharmacokinetic property might explain its requirement for higher dosage in reducing ALT and AST levels.

The liver is a major organ responsible for metabolizing several substances which may produce reactive oxygen species (ROS) promoting oxidative stress. In patients with NAFLD, there is impairment of mitochondrial β-oxidation of fatty acids due to the functional and structural alteration produced by the clinical disease itself. This state causes further accumulation of ROS, thereby resulting in more hepatic

damage. In this light, the essential role of L-carnitine in the transfer of the long-chain fatty acids inside the mitochondria for β-oxidation might be a reason for reducing ALT and AST levels, which are markers of liver integrity. On the other hand, deficiency of L-carnitine results in the reduction of fatty acid transportation to mitochondria and facilitates accumulation in the cytosol relating to the pathogenesis of insulin resistance and poor glycemic control.[15] In this study, we also assessed its effect on such parameter through comparison of fasting blood sugars and the result failed to show significant reduction as analyzed.

Furthermore, obesity has been highly associated with NAFLD. Steatosis or increase in intrahepatic triglyceride content is the hallmark feature of the disease. It occurs when there is imbalance on the rate of hepatic fatty acid uptake from plasma and its *de novo* synthesis. In this study, the role of L-carnitine was determined in improvement of anthropometric index through change in BMI. This presumption reverts back to the essential function of L-carnitine in mobilization of fatty acids. Unfortunately, no effect was demonstrated in the grouped analysis. Safety was one of the variables we aimed to look into; however, not one study included it in their analysis of data.

Conclusion

The use of either L-carnitine or carnitine-orotate complex demonstrated reduction of liver enzymes (AST, ALT) among patients with non-alcoholic fatty liver disease, although heterogeneity among groups remained to exist even after subgroup analysis based on treatment doses and durations. Moreover, the study also showed more significant AST reduction with higher doses (>500 mg/day) of the drug. This study has also proven that L-carnitine has no significant reduction on other metabolic profiles including body mass index as well as glycemic control through FBS monitoring, as determined by the statistical analysis.

Implications in Research

The emergence of L-carnitine as a potential therapeutic intervention among NAFLD patients and its inclusion in several clinical trials signifies its relevance in clinical practice. Hence, we highly recommend to increase the number of clinical subjects on future RCTs to formulate a more robust and reproducible evidence. Furthermore, direct outcomes including both histologic (the gold standard for the diagnosis of NAFLD) and imaging measures must be evaluated on top of the clinical parameters so that its use may well be translated into practice. Allowing more observation time and longer duration of treatment are also encouraged to further assess the effectiveness of the intervention.

Conflict of Interest

All PJG peer reviews are blinded. Dr. AD Salvaña, as co-author and at the same time member of PJG's editorial staff, inhibited herself from the review process and acceptance of this paper.

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