THE ROLE OF L-CARNITINE IN THE IMPROVEMENT OF LIVER FUNCTION AND GLYCEMIC CONTROL AMONG PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE: A META-ANALYSIS

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ABSTRACT

Significance: Population-based cohort studies from Asia reported rising prevalence of NAFLD ranging from 10% to 24% resembling a local study with a rate of 12.2% with obesity (56%) and diabetes mellitus (69%) as important comorbidities. Various therapeutic interventions have emerged to address this disease hence we aim to pool data from randomized controlled trials to assess the role of carnitine in improving liver function and glycemic control among NAFLD patients.

Methodology: A search from electronic databases including PubMed, Cochrane Library and Google Scholar was made obtaining five randomized controlled trials. Studies included adult patients $\geq$18 years old with non-alcoholic fatty liver disease diagnosed through clinical and/or histologic findings. Non RCTs including retrospective study and case reports were excluded. Methodologic assessment of studies and statistical analaysis were performed through Review Manager version 5.3.

Results: Of 33 studies identified, 5 fulfilled the inclusion criteria which entailed 340 clinical subjects. The 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$9.88 (*p*-value= 0.0005) respectively. No significant reduction on BMI and fasting blood sugar was demonstrated with mean differences of -0.10$\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 more significant reduction with carnitine dose of >500mg/day.

Conclusion: The use of L-carnitine showed great potential in improving liver function but not glycemic control and BMI among patients with NAFLD. Further studies involving more clinical subjects, histologic and radiologic assessments are highly recommended.

Keywords: carnitine, carnitine-orotate, non-alcoholic fatty liver disease, non-alcoholic staeatohepatitis, 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 setting as evidenced by a cohort study published last 2008 stating a 12.2% rate of NAFLD diagnosed 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 comorbidites that highly contributes 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 "2-hit" hypothesis by which sequential progression from isolated fatty liver (IFL) to 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 highy 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 2-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, detoxication 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 acids 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 function and glycemic control among patients with NAFLD. Hence the aim of this study is to synthesize data from pooled randomized controlled trials involving this emerging intervention.

Research Question:

Among patients with non-alcoholic fatty liver disease, how effective is the use of L-carnitine in the improvement of liver function and glycemic control?

Objectives

General Objective:

To assess the effects of L-carnitine in the improvement of liver function and glycemic control among patients with Non-alcoholic fatty liver disease

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 glycemic control through serial FBS monitoring among patients with non-alcoholic fatty liver disease treated with L-carnitine versus the control group
3. To determine the effects of L carnitine on other anthropometric profiles including BMI
4. To determine any possible adverse effects related to L-carnitine among patients with non-alcholic fatty liver disease if available

Methodology

Database and search strategy

Electronic databases including PubMed, Cochrane Library and Google Scholar were used to to retrieve articles from January 1986 when the drug was approved by the U.S.FDA for public use up to November 2019. The search terms/keywords used were: (L-carnitine, carnitine, carnitine-orotate, NASH, nonalcoholic 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 reference 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 conducted among adult patients ≥18years of age with non-alcoholic fatty liver disease; use of either oral or IV 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, fasting blood sugar, body mass index and other metabolic profile if available. Studies which are non RCTs including retrospective study and case reports or reviews were excluded. Subsequently, patients known to have alcoholic fatty liver disease and significant alcohol consumption (male 20g/day and female 10g/day); hepatocellular carcinoma or cirrhosis related to other etiologies were also not included in the selection.

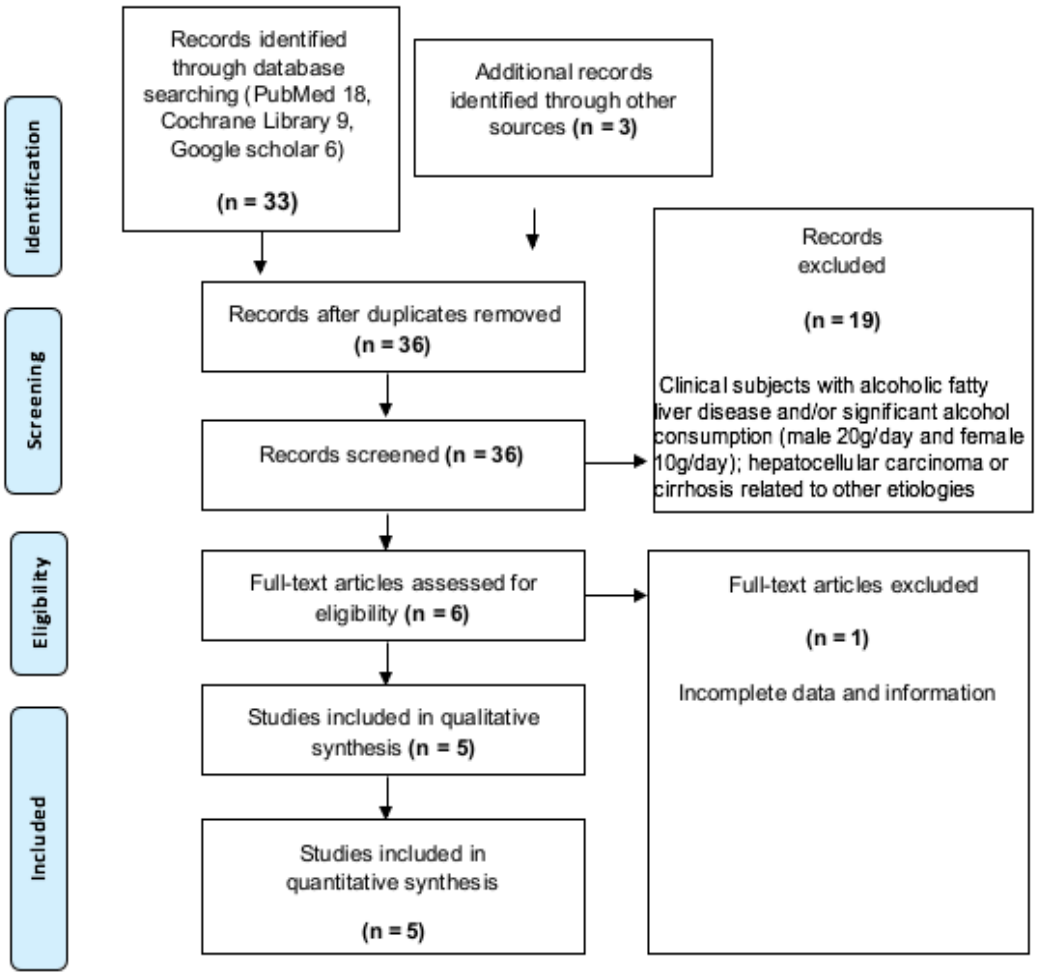
Selection of studies:

The study included trials discussing treatment effect 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 non-alcoholic fatty liver disease. 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.

A comprehensive literature search was performed and was able to identify 33 references from various

electronic databases including the following; PubMed=18, Cochrane Library=9 and Google Scholar=6. Three additional article was retrieved through hand search. Out of the 33 articles, 6 studies were fully reviewed and assessed for eligibility. One study was excluded due to lack of necessary data and information despite reaching the inverstigators. Hence, this resulted in the analysis of 5 randomized controlled studies. (Figure 1).

FIGURE 1: Flow diagram for 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 RevMan 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 was classified as to either low, high or unclear risk of bias. The qualities of the 5 randomized studies are summarized in Fig 2 and 3. Overall, there is essentially low risk of bias for most of the domains except for the method of allocation concealment which was not stated in majority of the RCTs included.

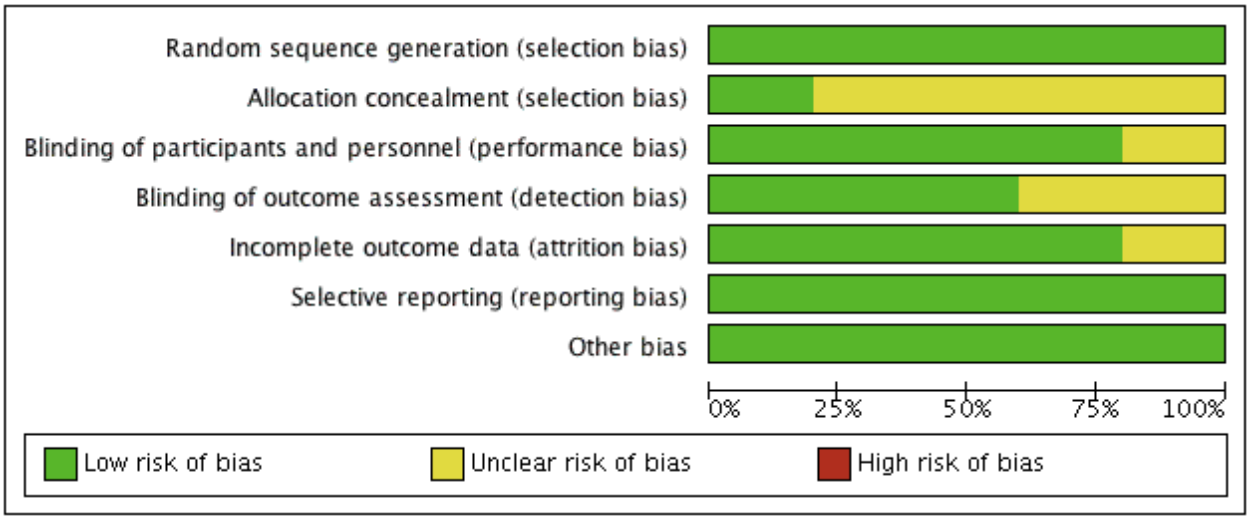
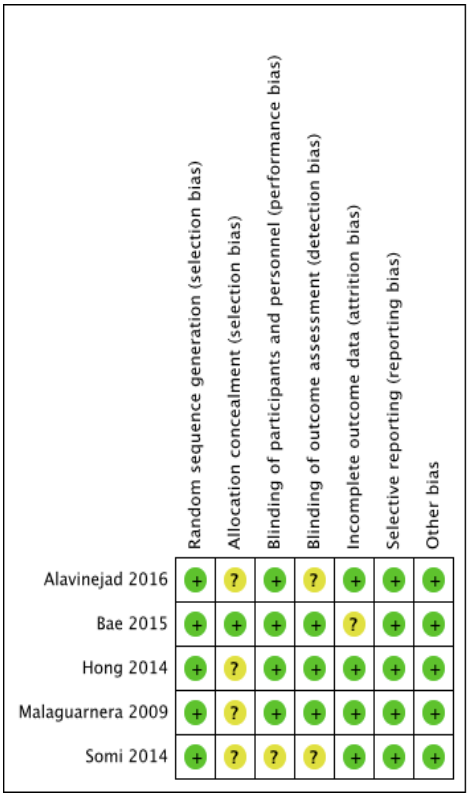


Fig 2. Risk of bias graph of the included randomized controlled trials



Statistical analysis

All statistical analyses were performed using RevMan 5.3 that is provided by The Cochrane Collaboration. Heterogeneity was assessed using the chi-square statistic and a P value of less than 0.05 was considered to represent significance. The statistical strength was identified by overall effect size Z and the degree of heterogeneity was determined by the I^2 value. Additionally, sensitivity analyses that were conducted to determine the stability of the overall effects were performed by the random effects model.

RESULTS

Characteristic 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 function and glycemic control are shown in Table 1. Five studies presented results on improving liver function test as well as other metabolic parameters as outcomes including gylcemic control and BMI. Various doses and frequency of either L-carnitine or carnitine orotate were used in the study ranging from 300mg/day to 2,342mg/day. Majority of the studies had a treatment duration of 90 days except for two studies extending up to 24 weeks or 180 days.

Table 1. Baseline Characteristics of Included Studies

	RCT1 Malaguarnera et al[7] (2009)	RCT2 Hong et al[8] (2014)	RCT 3 Bae et al[9] (2015)	RCT Alavinejad et al[10] (2017)	RCT 5 Somi et al[11] (2016)
Age	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	110.5/109.8	141/147.8	143.6/153.4	172/175	NS
ALT	120.2/125.7	71.2/67.1	94.9/79.2	124/120	81.7/54.1
AST	135.4/132.8	44.3/44.4	61.8/51.7	122.7/125.3	60.5/52.6
Treatment Duration	180 days	90 days	90 days	90 days	180 days
Treatment Dosage	L-carnitine 2000mg/day	Carnitine-orotate complex 2 tabs TID (300mg/day)	Carnitine-orotate complex 824mg/TID (2,472mg/day)	L-carnitine 750mg/day	L-carnitine 500mg/day
Outcomes measured	ALT, yGTP, Albumin, Lipid profile, Insulin, C peptide, CRP, ALP	Primary: ALT; Secondary: FBS, Hba1c, AST, mtDNA, 8hydroxydeoxyguanine	Primary: Decline in ALT to normal range; Secondary: Hepatic steatosis using HU via noncontrast 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
Number of Participants	36/38	24/24	39/39	30/30	40/40

The baseline clinical characteristics of the participants in each trial were demonstrated as well with an age ranging approximately from 40 to 60 years old. The total number of pooled subjects from the clinical trial summed up to 340 patients with 169 (49.7%) and 171 (50.3%) for the treatment and control groups respectively. There are 234 (68.82%) male subjects and 106 (31.2%) female participants. Of note is 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 Outcome

Change in serum ALT levels

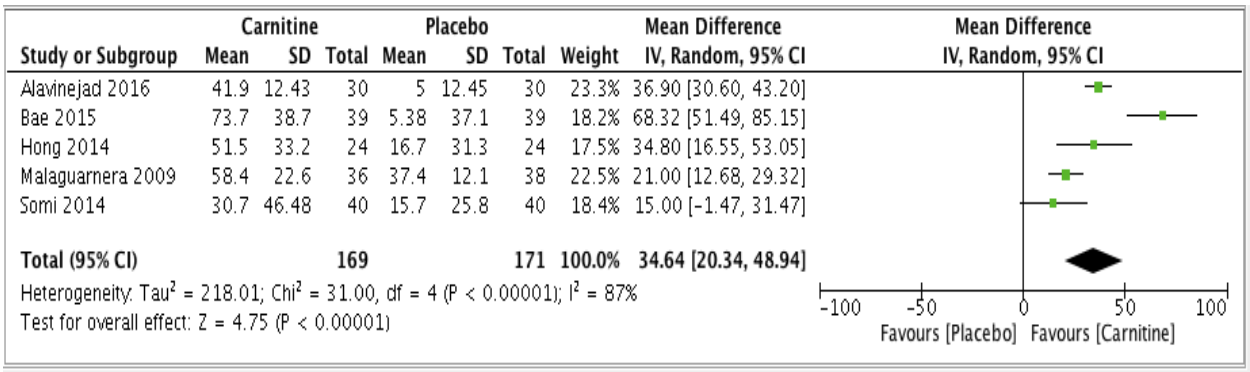


Fig 4. Forest plot on the change of serum ALT from baseline between treatment (carnitine) and control goup

The pooled analysis using the 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%.

Change in serum FBS level

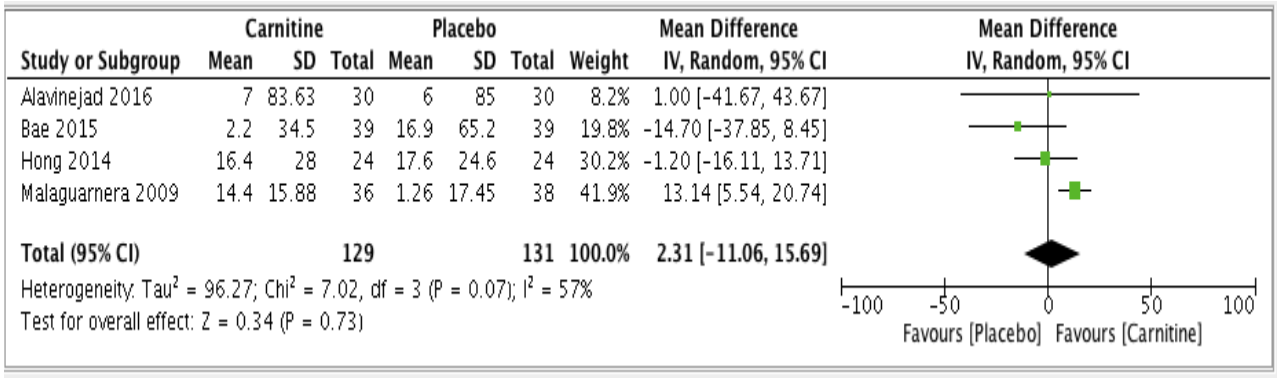


Fig 5 . Forest plot on the change of Fasting blood sugar from baseline between treatment (carnitine) and control goup

Four studies were included in the grouped 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.

Secondary outcomes

Change in AST levels

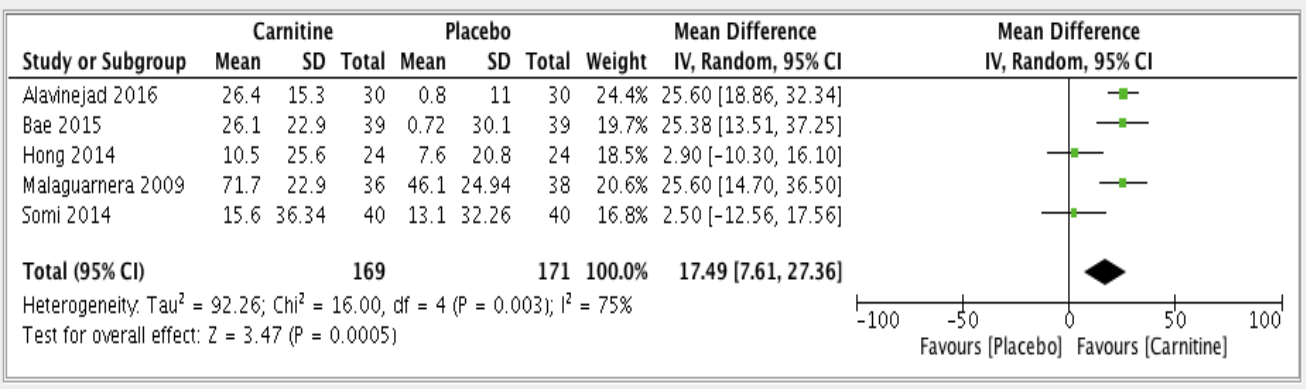


Fig 6. Forest plot on the change of serum AST from baseline between treatment (carnitine) and control goup

Grouped analysis of included trials evaluating change in serum AST levels among patients on the experimental 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%

Change in Body Mass Index (BMI)

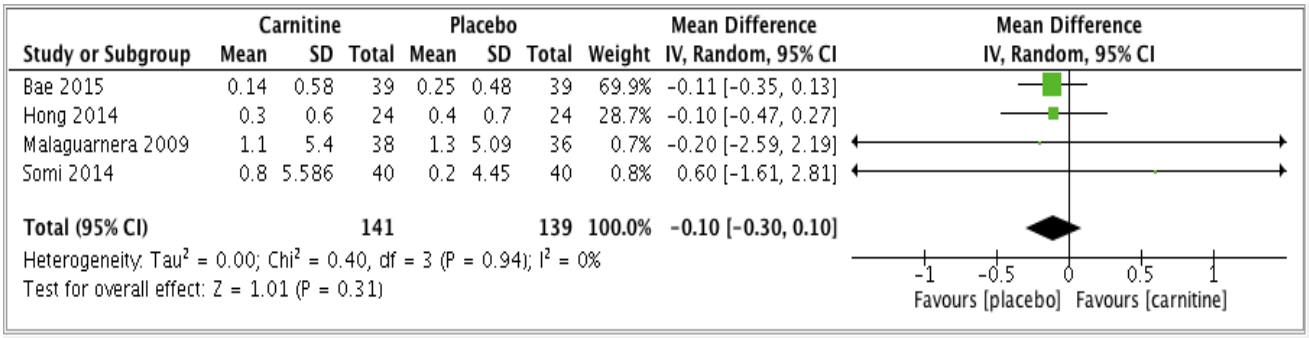


Fig 7. Forest plot on the change of BMI from baseline between treatment (carnitine) and control goup

Out of the 5 studies, there are 4 RCTs that evaluated the use of L-carnitine in the improvement of anthropometric measurement including body mass index 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 homogenous with a Chi square value of 0.40 and I^2 of 0%.

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 <500mg/day and >500mg/day. Treatment durations were divided into 90 and 180 days accordingly.

	No. of Studies	Weighted Mean Difference (95% CI)	*p-value* within group	*p-value of* heterogeneity	I^2
Change in serum ALT					
Treatment dose					
>500mg/day	3	48.21 (29.96 , 66.46)	0.00001	0.003	0.83
≤500mg/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

Table 2. Subgroup analysis comparing the effects of L-carnitine to serum ALT level based on treatment dose and duration

Change in serum ALT levels

The pooled analysis revealed that significant reduction in ALT remained unaltered regardless of the treatment dose and duration. Between doses of >500mg/day and ≤500mg/day, ALT is still signifcantly 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, improvent in serum ALT is still achieved with a weighted mean difference of 19.78 (p-value of <0.00001) in 180 days. However, this is grossly less compared to the pooled analysis of 3 studies with treatment duration of 90 days with a weighted mean difference of 46.05 (p-value of <0.00001).

	No. of Studies	Weighted Mean Difference (95% CI)	*p-value* within group	*p-value of* heterogeneity	I^2
Change in serum Fasting Blood Sugar					
Treatment dose					
>500mg/day	3	2.21 (-18.05, 22.47)	0.83	0.07	0.62
<500mg/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

Table 3. Subgroup analysis comparing the effects of L-carnitine to serum FBS level based on treatment dose and duration

Change in serum FBS level

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

	No. of Studies	Weighted Mean Difference (95% CI)	*p-value* within group	*p-value of* heterogeneity	I^2
Change in serum AST					
Treatment dose					
>500mg/day	3	25.56 (20.39 , 30.72)	<0.00001	1.0	0.0
<500mg/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

Table 3. Subgroup analysis comparing the effects of L-carnitine to serum AST level based on treatment dose and duration

Change in serum AST level

In this analysis, AST was proven to be more significantly reduced with the use of L-carnitine at dosage of >500mg/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 <500mg/day (WMD: 2.73 (-7.20 , 12.65); p-value 0.59). Furthermore, the use of L-carnitine for 90 days showed greater reduction in AST than treatment for 180 days.

Safety

Of the five studies included in the analysis, none measured or evaluated safety or adverse event as an outcome of interest.

DISCUSSION

Apart from diet and lifestyle modification, various pharmacologic interventions already emerged and have been studied to assess its 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 function including AST, ALT and other metabolic profiles including glycemic control (fasting blood sugar) and anthrophometric index (BMI) among patients with non-alcoholic fatty liver disease. 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 to 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 greater achieved with a dose of

>500mg/day. The oral supplementation of L-carnitine (1–6 g) has been reported to only have a biological availability between 5 to 18%. This limited bioavailability is associated with the metabolization of L-carnitine by the 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 non-alcoholic fatty liver disease, 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 to 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, deficieny of L-carnitine results in the reduction of fatty acid transportation to mitochondira 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 the 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 acid. Unfortunately, no effect was demonstrated in the grouped analysis. Safety is one of the variables we aimed to look into; however, none of the studies retrieved included it in their analysis of data.

CONCLUSION

In conclusion, the data among pooled studies showed a significant effect on the use of either L-carnitine or carnitine-orotate complex in the reduction of liver enzymes among patients with non-alcoholic fatty liver disease across all treatment doses and duration. Moreover, the study also showed more significant AST reduction with higher doses (>500mg/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 which is 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 be well-translated in practice. Allowing more observation time and longer duration of treatment are also encouraged to further assess the effectiveness of the intervention.

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