International Journal for Vitamin and Nutrition Research

Int. J. Vitam. Nutr. Res. **2025**; 95(2): 40033
https://doi.org/10.31083/IJVNR40033

Review

The Effect of the L-Carnitine Supplementation on Obesity Indices: An Umbrella Meta-Analysis

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Academic Editor: Torsten Bohn
Submitted: 29 August 2023 Revised: 15 April 2024 Accepted: 5 September 2024 Published: 28 April 2025

Abstract

Aims: Obesity, one of the most frequent health risks, represents a global public health problem. The potential impact of L-carnitine, a vital nutrient for energy metabolism, on weight loss is worth considering. However, given the inconclusive results from recent meta-analyses on L-carnitine, we conducted an umbrella meta-analysis of placebo-controlled and controlled trials to evaluate the effect of L-carnitine on anthropometric indices. **Methods**: Data synthesis: A comprehensive search approach using the relevant keywords was performed in PubMed, Web of Science, Scopus databases, and Google Scholar up to March 2023. Meta-analyses published in English that provided quantitative statistical analyses regarding the effects of L-carnitine on body weight, waist circumference (WC), and body mass index (BMI) were included. A random-effects model and subgroup analysis were performed based on the L-carnitine dosage and study population. **Results**: A total of 16,352 participants were included. Intervention durations ranged from 8 to 30 weeks, with L-carnitine dosages ranging between 150 and 4000 mg/day. The pooled results of the eight included meta-analyses indicated that L-carnitine supplementation can significantly decrease weight (effect size (ES) = –1.11; 95% confidence intervals (CIs): –1.90, –0.33, p = 0.005; I^2 = 90.6%, $p < 0.001$), BMI (ES = –0.33; 95% CI: –0.61, –0.04, p = 0.026; I^2 = 89.8%, $p < 0.001$), and WC (ES = –1.34; 95% CI: –1.83, –0.85, $p < 0.001$; I^2 = 00.0%, p = 0.442). **Conclusion**: The findings of this umbrella meta-analysis support that supplementation of L-carnitine supplementation can successfully manage weight, BMI, and WC reduction. Therefore, L-carnitine might help treat obesity. **PROSPERO Registration Number**: CRD42022307951.

Keywords: body weight; body mass index; waist circumference; weight loss; lipotropic supplementation; anthropometric

1. Introduction

Obesity, as one of the most frequent health risks, is a public health problem in the general population around the world [1]. Based on the World Health Organization (WHO) reports, 39% of worldwide adults were overweight and 13% were obese in 2016. Globally, the prevalence of obesity has nearly tripled from 1975 to 2016 [2]. Body mass index (BMI) and waist circumference (WC) are simple indices commonly used to classify overweight and obesity in adults and predict obesity-related health risks [3,4]. Obesity is a chronic disorder that is associated with developing non-communicable diseases [5]. In fact, increased BMI is a major risk factor for diabetes, cardiovascular diseases, some cancers, and many other non-communicable diseases and play role in increasing premature death and disability in adulthood [6]. It also has been reported that medical costs for obese people are higher than people with healthy weight [7]. There are different approaches for obesity management such as lifestyle modifications and pharmacological or herbal interventions [8]. Although there are various dietary supplements for weight management on the market, there is not sufficient evidence regarding their effectiveness [9,10]. L-carnitine is one of the supplements claimed to be efficacious on weight loss [11].

Carnitine or beta-hydroxy-gamma-methyl ammonium butyrate is a hydrophilic molecule which consists of two amino acids: lysine and methionine. Carnitine is a necessary nutrient for energy metabolism as it is necessary for the transfer of fatty acids into the mitochondria for beta-oxidation and energy production. It also has an important role in reactive oxygen species formation, energy production, trapping acetyl groups, and the metabolism of glucose [12], and through these, carnitine may be involved in weight loss or gain [13]. Dairy and animal proteins serve as primary sources of exogenous carnitine. Additionally, the kidneys and liver synthesize this essential nutrient [14,15]. Research indicates that carnitine transported from the intestinal lumen into the enterocyte, then passes across the serosal membrane into the circulation through simple diffusion [16]. Studies have reported several benefits of car-

nitine supplementation including: reducing inflammation, improving lipid profile, improving quality of life, antioxidant effects, and weight control [17–21].

It has been shown in recent studies that L-carnitine supplementation plays a role in improving insulin resistance and appetite suppression by affecting hypothalamic carnitine palmitoyl transferase [22,23]. L-carnitine has also demonstrated lipid-lowering activities and blood glucose control [24]. Through these proposed mechanisms, carnitine supplementation could be effective in obesity management and weight loss [22–24]. While some meta-analyses studies reported beneficial effects of L-carnitine supplementation on weight loss [11,25–28], conflicting findings have been observed in other studies [29,30]. Ko *et al*. [31] were also unable to demonstrate a favourable impact of L-carnitine intervention on the reduction of body weight and BMI in their recent meta-analysis. The results of meta-analyses regarding the effects of L-carnitine on WC also present inconsistencies [25,26]. Due to the contradictory results of studies, it seems necessary to determine the role of carnitine supplementation in weight control and achieve a definite result. Thus, the present umbrella meta-analysis was conducted to determine the overall role of carnitine supplementation on anthropometric indices including weight, WC and BMI.

2. Methods

2.1 Literature Search

This research adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Cochrane handbook for systematic reviews of interventions [32,33]. Scientific databases including Scopus, PubMed, Web of Science, and Google Scholar were searched from inception up to March 2023. The applied MeSH terms and keywords were as the following: (carnitine) OR (acetylcarnitine) OR (ALCAR) OR (LCAR) OR (L-CAR) OR (L-car[tiab]) OR (Acetyl-L-Carnitine) OR (L-carnitine) OR (levocarnitine) OR (ACAL) OR ("acetyl carnitine") AND ("waist circumference") OR ("body weight") OR (obesity) OR (anthropometry) OR (overweight) OR ("body mass index") OR ("body size") OR ("body composition") OR (anthropometric) OR (BMI) AND ("meta-analysis").

2.2 Eligibility Criteria

We included all meta-analysis studies investigating the effects of carnitine supplementation on weight, BMI, and WC in both diseased and healthy adult populations which have reported the effect sizes (ES) and corresponding confidence intervals (CI). In addition, we excluded *in vivo*, *ex vivo*, and *in vitro* studies, quasi-experimental studies, observational studies, controlled clinical trials, case reports, and studies with low-quality scores, and limited the studies to those written in English.

2.3 Study Selection and Data Extraction

The screening process was conducted by two of the reviewers (FH and PJ) independently, and disagreements were resolved by discussion with the third reviewer (MZ). To ensure that all eligible articles were included in the study, the reference lists of all of the included meta-analyses were screened to identify relevant studies for systematic reviews. The first author's name, year and location, sample size, the type and dosage of carnitine supplementation and supplementation duration, ESs, and CIs for weight, BMI, and WC were extracted from the included meta-analyses after screening. We also extracted data related to the quality of included studies to use in the AMSTAR questionnaire to evaluate quality of studies. The AMSTAR contains 11 items and the maximum score is 11 [34]. Scores of 8–11, 4–7, and 0–3 points are rated as high, medium, and low quality, respectively (**Supplementary Table 1**).

2.4 Data Synthesis and Statistical Analysis

The overall effect sizes were calculated using ESs and CIs. We assessed heterogeneity based on I^2 statistics and Cochrane's Q-test. I^2 value $>50\%$ or $p < 0.1$ for the Q-test was considered as significant heterogeneity across the studies [35]. Random-effects model was employed to estimate the overall effect size using restricted maximum likelihood (REML) method. Subgroup analysis by duration and supplementation dosage variables were performed to find probable sources of heterogeneity. Sensitivity analysis was conducted to assess whether the overall effect size is influenced by removal of a single study. The small-study effect was evaluated by the formal Begg's test [36]. We assessed the publication bias via visual inspection of the funnel plots if the number of included studies was ≥ 7 and where the publication bias was observed, trim and fill analysis was performed. All analyses in this study were performed using the Stata, version 16 (Stata Corporation, College Station, TX, USA). A *p*-value less than 0.05 was considered statistically significant.

3. Results

3.1 Systematic Review

In the initial search, 117 studies were obtained. After discarding duplicates and screening of remaining studies, overall, nine meta-analyses published between 2013 and 2021 were included in the umbrella meta-analysis. The flow chart of the selection process is summarized in Fig. 1. 16,352 participants were included in this review, and the age range of participants was between 18 and 82 years. Five studies were conducted in Iran [11,27–30], one in Korea [25], one in Spain [37], one in China [26], and one in the USA [31]. Nine studies were included in the qualitative synthesis and 8 studies were included in the quantitative synthesis. Gholipour's meta-analysis study was not considered for quantitative analysis due to reporting the results

Table 1. Study characteristics of included meta-analyses for an umbrella meta-analysis assessing the effects of L-carnitine supplementation on weight, BMI, and WC.

Author, year	No. of studies in meta-analysis	Duration	No. of participants in meta-analysis	Mean Age/range (year)	Study population/weight condition	Intervention/Dosage range (mg/day)	Measured variables	Type of study	Quality Assessment Scale
Talenezhad *et al*. 2020	37	3–48 wk	2292	41/18–80	Different conditions[1]/Mix of weight conditions	L-carnitine/250–4000	Weight, BMI[6], WC[7]	Controlled trials/placebo-controlled trials	Yes (Cochrane)
Abolfathi *et al*. 2019	5	12–24 wk	280	47/39–60	NAFELD[2]/Not Reported (NR)	L-carnitine an carnitine orotate/300–2000	Weight, BMI	Controlled trials/placebo-controlled trials	Yes (Jaded scale)
Gholipur *et al*. 2018	5	12–24 wk	293	NR	CKD[3]/NR	L-carnitine/750–1500	Weight, BMI	Controlled trials/placebo-controlled trials	Yes (Cochrane)
Pooyandjoo *et al*. 2016	9	4–52 wk	911	42/20–82	Different conditions/Mix of weight conditions	L-carnitine/1000–4000	Weight, BMI	Controlled trials/placebo-controlled trials	Yes (Jaded scale)
Askarpour *et al*. 2019	45	2–52 wk	9596	42/23–82	Different conditions /Overweight & Obese	L-carnitine/600–4000	Weight, BMI, WC	Placebo-controlled trials	Yes (Cochrane)
Liao *et al*. 2021	6	12 wk	672	27/24–31	PCOS[4]/Overweight & Obese	L-carnitine/150–1000	Weight, BMI, WC	Placebo-controlled trials	Yes (Cochrane)
Vidal-Casariego *et al*. 2013	3	NR	NR	NR	DM[5]/NR	L-carnitine/2000–3000	Weight, BMI	Placebo-controlled trials	Yes (Jaded scale)
Choi *et al*. 2020	2	8–12 wk	155	48/41–68	Metabolic Syndrome/NR	L-carnitine/750–3000	WC	Placebo-controlled trials	Yes (Cochrane)
Ko *et al*. 2022	11	4–48 wk	2153	NR	DM/NR	L-carnitine/900–2000	Weight, BMI	Controlled trials/placebo-controlled trials	Yes (Cochrane)

1: Different Conditions like: DM, hepatitis c, NAFELD, etc.
2: Non-Alcoholic Fatty Liver Disease.
3: Chronic Kidney Disease.
4: Polycystic Ovary Syndrome.
5: Diabetes Mellitus.
6: BMI, Body Mass Index.
7: WC, Waist Circumference.

in a different unit from the one reported in the rest of the studies [30]. Gholipur-Shahraki *et al*. [30], evaluated the effect of L-carnitine on patients with chronic kidney disease and reported no conclusive effect of carnitine on body weight and BMI [30]. The total number of registered clinical trials (RCTs) included in our meta-analyses was 118 studies. The mean duration of interventions varied from 8 to 30 weeks, and dosage range of L-carnitine was between 150 and 4000 mg/day. Of nine meta-analyses that evaluated the quality of included studies, three cases used the Jadad quality assessment scale and six cases used the Cochrane Risk of Bias Tool scale. Table 1 provides the details of included studies reviewed.

3.2 Risk of Bias Assessment

Based on the AMSTAR questionnaire, all included meta-analyses studies were evaluated as high quality. The quality score of seven studies was 11 and two cases had a quality score of 10 due to no assessment of publication bias. The results are presented in **Supplementary Table 1**.

3.3 The Effects of L-carnitine Supplementation on Weight

The results from analysis of six studies indicated that the supplementation of carnitine significantly reduced weight (ES = –1.11 kg; 95% CI: –1.90, –0.33, $p = 0.005$; $I^2 = 90.6\%$, $p < 0.001$) (Fig. 2). Reduction in weight was attributed to a subgroup of dosage >1000 mg/day (ES = –0.89 kg; 95% CI: –1.51, –0.27). Also, the reduction of body weight by carnitine supplementation was more pronounced with study duration of <18 weeks (ES = –1.74; 95% CI: –2.92, –0.66) (Table 2). The results of sensitivity analysis indicated that no study's removal affected the overall effect size.

3.4 The Effects of L-carnitine Supplementation on BMI

The pooled results of the seven meta-analyses showed that the supplementation of carnitine significantly decreased BMI values (ES = –0.33 kg/m^2; 95% CI: –0.0.61, –0.04, $p = 0.026$; $I^2 = 89.8\%$, $p < 0.001$) (Fig. 3A). In the subgroup analysis, dosage and duration of carnitine supplementation had no significant effects on BMI reduction (Table 2). Sensitivity analysis showed that the exclusion of three studies affected the overall effect size (Talenezhan, Askarpour, and Pooyandjoo) (ES = –0.34; 95% CI: –0.73, 0.04 and ES = –0.32; 95% CI: –0.68, 0.03, ES = –0.30; 95% CI: –0.62, 0.01 respectively). Visual inspection of the funnel plot (Fig. 3B) showed an uneven distribution of studies; therefore, trim and fill analysis were conducted (with three imputed studies) and the results remained consistent, showing that carnitine significantly reduced BMI values (ES = –0.60; 95% CI: –0.94, –0.26, $p < 0.05$)

3.5 The Effects of L-carnitine Supplementation on WC

Four meta-analyses investigated effect of L-carnitine on WC and all of them were included in the analysis. The supplementation of L-carnitine significantly reduced WC (ES = –1.34; 95% CI: –1.83, –0.85, $p < 0.001$; $I^2 = 00.0\%$, $p = 0.442$) (Fig. 4). The results of sensitivity analysis indicated that no study's removal affected the overall effect size. Subgroup analysis due to small number of studies was not performed.

4. Discussion

Obesity and overweight are growing health problems worldwide and are linked to several chronic diseases [38–40]. Various treatments have been studied and utilized in the treatment for obesity and overweight condition [41]. Effective and safe treatment plans for obesity commonly involve a change in lifestyle (i.e., behavioural, physical, and nutritional) and, in some cases, weight loss supplements are prescribed as a complementary treatment [42]. L-carnitine supplementation has been studied for its lipotropic effects under several disease states [24,43], and, specifically, for its potential benefits in reducing weight in obese and overweight individuals [25,26,30].

This umbrella review supports the effects of supplementation with L-carnitine on reducing weight, BMI, and WC. Out of the six meta-analyses included in the analysis of the effect of L-carnitine on weight reduction, four concluded similar findings [11,26–28], while two failed to demonstrate this effect [29,31]. The same applies to BMI as well. Seven studies examined the effect of L-carnitine on BMI, of which four studies [11,26–28] had consistent results with the present study and three of them [29,31,37] had inconsistent results.

One of the potential causes for these differences could be the study population: Abolfathi *et al*. [29], investigated L-carnitine supplementation on weight and BMI in individuals with nonalcoholic fatty liver disease (NAFLD), and participants in the studies by Ko *et al*. [31], and Vidal-Casariego *et al*. [37] were diabetic, and each study had a specific study population. In some meta-analysis [11,27,28], studies with different populations, including both healthy and diseased individual with normal weight or obesity were investigated. In the subgroup analysis of some included studies for present umbrella-meta analysis [28,31], a tendency toward decreased weight with L-carnitine supplementation was observed, with an increase of BMI and body weight. Together, these indicate a potentially favorable impact of L-carnitine on patients with higher baseline body weight and BMI. Furthermore, in an interventional animal study conducted by Shoveller *et al*. [44], overweight cats in positive energy balance fed diets supplemented with L-carnitine exhibited lower body fat deposition than lean cats supplemented with L-carnitine. Therefore, it appears that L-carnitine supplementation may be more effective in obese and overweight individuals, and body fat mass or energy intake may influence outcomes.

According to the present study body weight in a subgroup of <18 weeks of intervention duration had a more

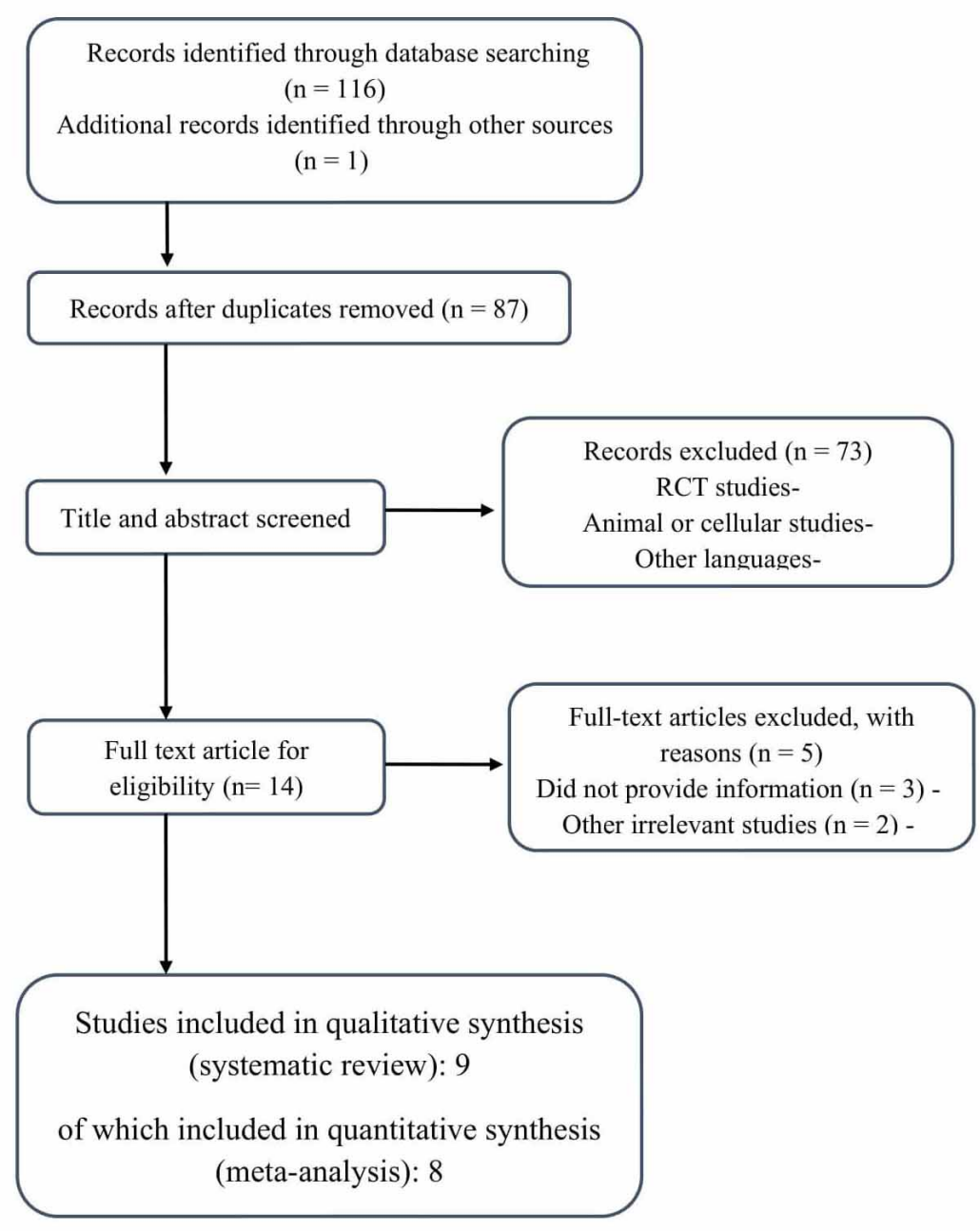

Fig. 1. Flow diagram depicting overview of the study-selection process.

pronounced decreasing effect. This may be attributed to decreasing adherence as the intervention duration increases.

Another potential cause for the discrepancy in the findings between the present study and the studies of Abolfathi *et al*. [29] and Vidal-Casariego *et al*. [37] could be the small number of analyzed RCTs and, as a result, the small sample size. Additionally, according to Abolfathi *et al*. [29], low-quality RCTs were included for data analysis, and carnitine deficiency at baseline was not evaluated among the studies. There are also some concerns regarding the study of Pooyandjoo *et al*. [11]. This study included RCTs with co-intervention in addition to L-carnitine. Therefore, the observed results might not reflect the pure effect of L-carnitine [45]. Additionally, one eligible study has been inadvertently excluded from the analysis due to using a different unit than that reported in the rest of the studies [30], which could affect the results. Additional studies are needed to validate these findings.

In the current study, the reduction in WC attributed to L-carnitine supplementation is supported by the results of the analysis. Two meta-analyses [25,26] demonstrated the potential of L-carnitine to reduce WC, while the studies by Askarpour *et al*. [27] and Talenezhad *et al*. [28] failed to replicate this effect. In the subgroup analysis of the aforementioned studies, a significant reduction in WC was observed specifically in overweight and obese individuals. In

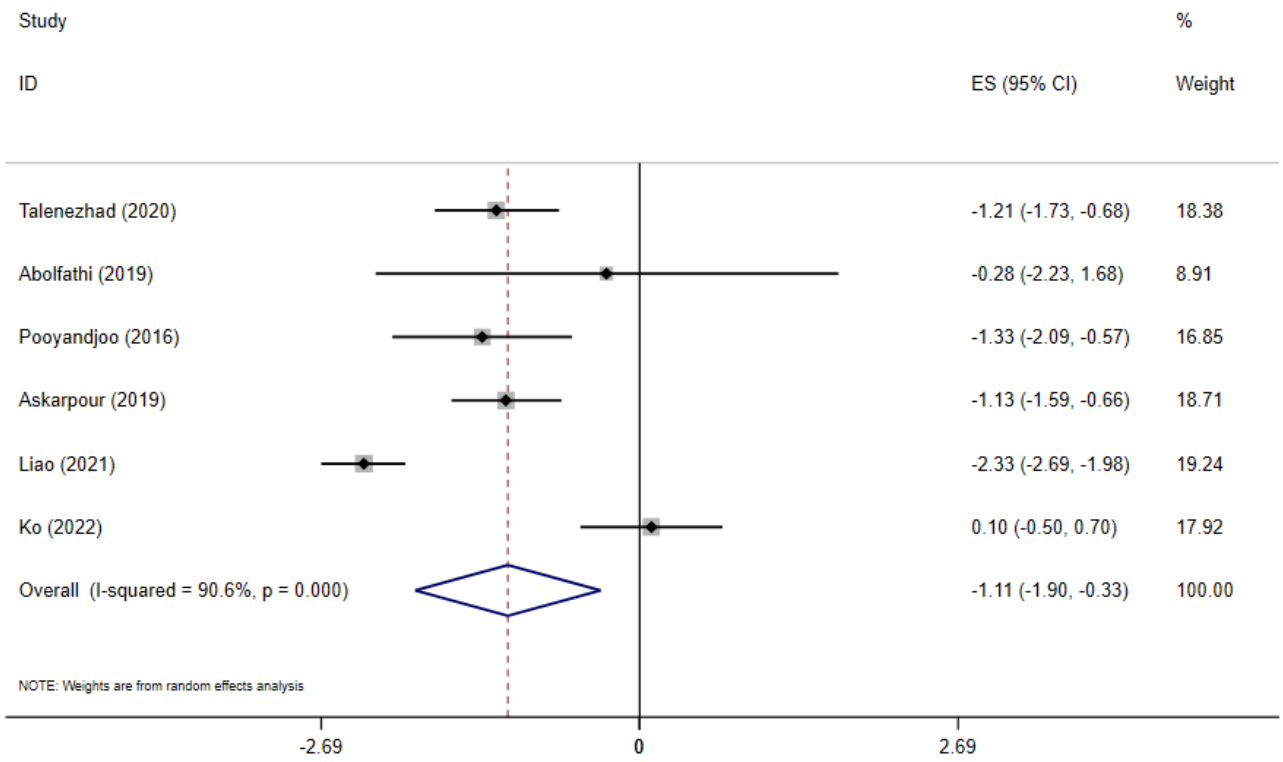

Fig. 2. Forest plot of the effects of L-carnitine supplementation on body weight detailing effect size (ES) and 95% confidence intervals (CIs).

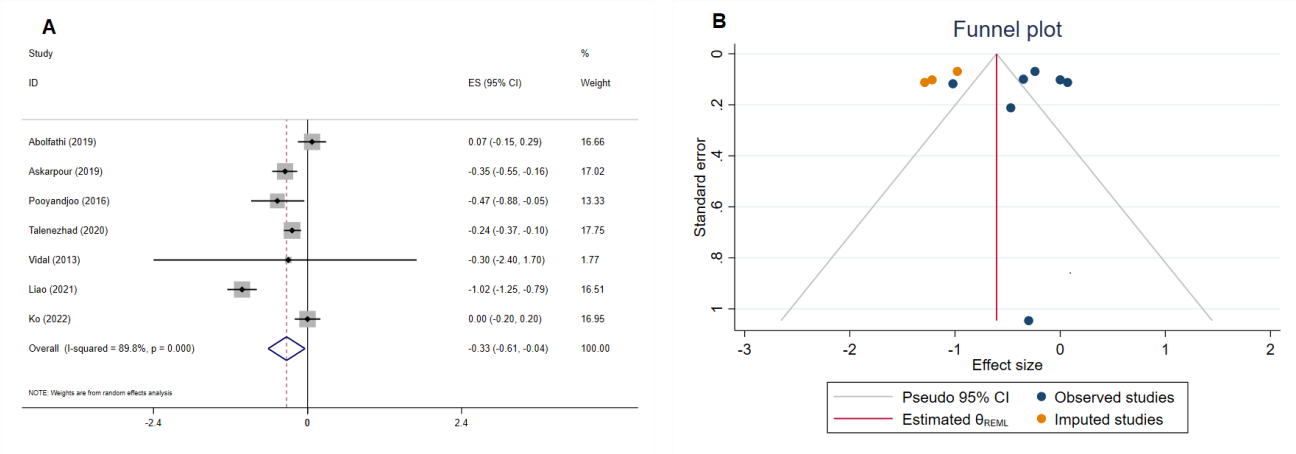

Fig. 3. The effects of L-carnitine supplementation on BMI. Forest plot (A) detailing ES and 95% CIs; Trim-and-fill analysis (B). ES, effect size; REML, restricted maximum likelihood method.

this case, it appears that the variation in study results can be attributed to differences in the study populations. WC is one of the criteria for metabolic syndrome and is also directly related to diseases such as polycystic ovary syndrome [46,47]. Therefore, interventions that aid in the reduction of WC could be effective in the improvement of various metabolic diseases under the metabolic syndrome.

The hypothesized mechanism for the reducing effect of L-carnitine on weight and BMI is shown schematically in Fig. 5. Fatty acids are stored in adipose tissue during periods of positive energy balance, and they are the major source of energy for vital organs of body [48]. Carnitine acetyltransferase enzymes (CATs) in the mitochondria, endoplasmic reticulum, and peroxisome use carnitine as a cofactor for transports of long-chain fatty acids across the inner mitochondrial membrane to stimulate β-oxidation in various cells, resulting in fatty acid

Table 2. Results of a subgroup analysis by dosage and intervention duration in an umbrella meta-analysis assessing the effects of L-carnitine supplementation on weight, and BMI.

	Effect size, *n*	ES (95% CI)	*p* – within	I^2 (%)	P-heterogeneity
L-carnitine supplementation on weight					
Overall	6	–1.11 (–1.90, –0.33)	0.005	90.6	<0.001
Dose (mg/day)					
>1000	4	–0.89 (–1.51, –0.27)	0.005	78.8	0.003
<1000	2	–1.54 (–3.50, 0.42)	0.123	75.5	0.043
Intervention duration (week)					
<18	2	–1.74 (–2.92, –0.66)	0.004	93.8	<0.001
≥18	4	–0.74 (–1.55, 0.07)	0.072	77.1	0.004
L-carnitine supplementation on BMI *					
Overall	7	–0.33 (–0.61, –0.04)	0.026	89.8	<0.001
Dose (mg/day)					
<2000	4	–0.38 (–0.77, 0.00)	0.051	93.9	<0.001
≥2000	3	–0.19 (–0.57, 0.19)	0.330	50.5	0.133
Intervention duration (week)					
<20	3	–0.39 (–0.94, 0.16)	0.160	95.9	<0.001
≥20	4	–0.24 (–0.50, 0.02)	0.069	61.2	0.052

p-value < 0.05 was considered statistically significant.

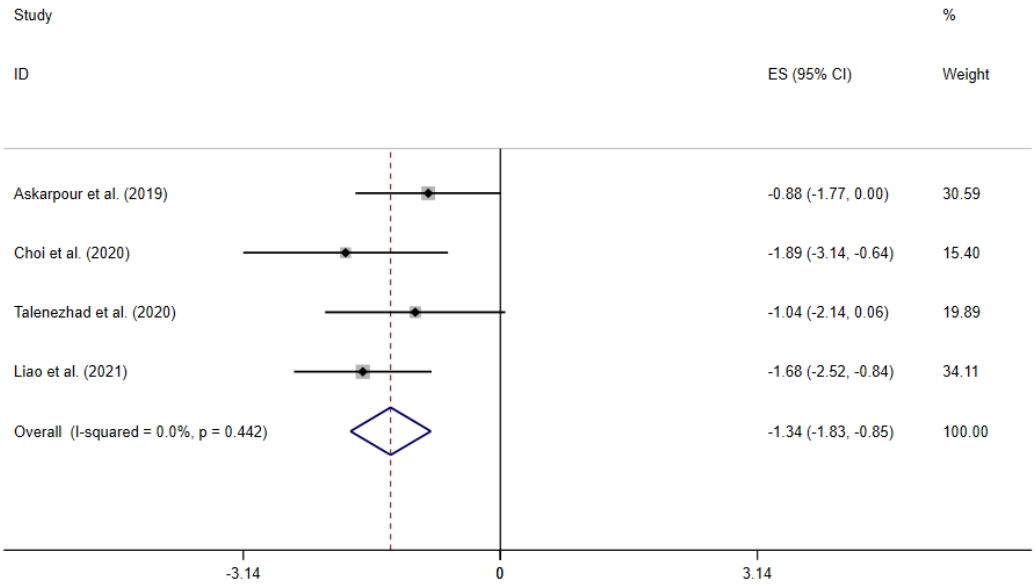

Fig. 4. Forest plot of the effects of L-carnitine supplementation on WC detailing ES and 95% CIs.

metabolism, energy production, and the utilization of fatty acid storage in the body [49]. Also, carnitine has a role in the activity of hormone-sensitive lipase, peroxisome proliferator-activated receptor-gamma (PPAR-γ), carnitine palmitoyl transferase 1-a, acyl-coenzyme A oxidase, and adipose-specific fatty acid-binding protein which cause lipid catabolism [50,51]. Carnitine inhibits the synthesis of fatty acids in the liver while stimulating mRNA synthesis and gene expression of PPARγ [52]. In peroxisome, carnitine octanoyl transferas (CTO) plays a main role in the β-oxidation of very long chain fatty acids, α-oxidation of phytic acid, and the formation and transfer of medium chain fatty acids to the mitochondrial matrix for β-oxidation [53,54]. Also, carnitine regulates energy expenditure by enhancing acetyl-coenzyme A concentration and glucose supply for brain metabolism [13,55]. An inverse effect of L-carnitine on food intake through suppressing the center of hunger in the hypothalamus along with a hypocaloric diet was reported in studies [23,56,57].

In accordance with existing recommendations, the established safe threshold for L-carnitine intake is up to 2000 mg/day. This limitation is imposed due to reported adverse effects, including nausea and stomach discomfort, as well as the formation of trimethylamine-N-oxide, a risk factor

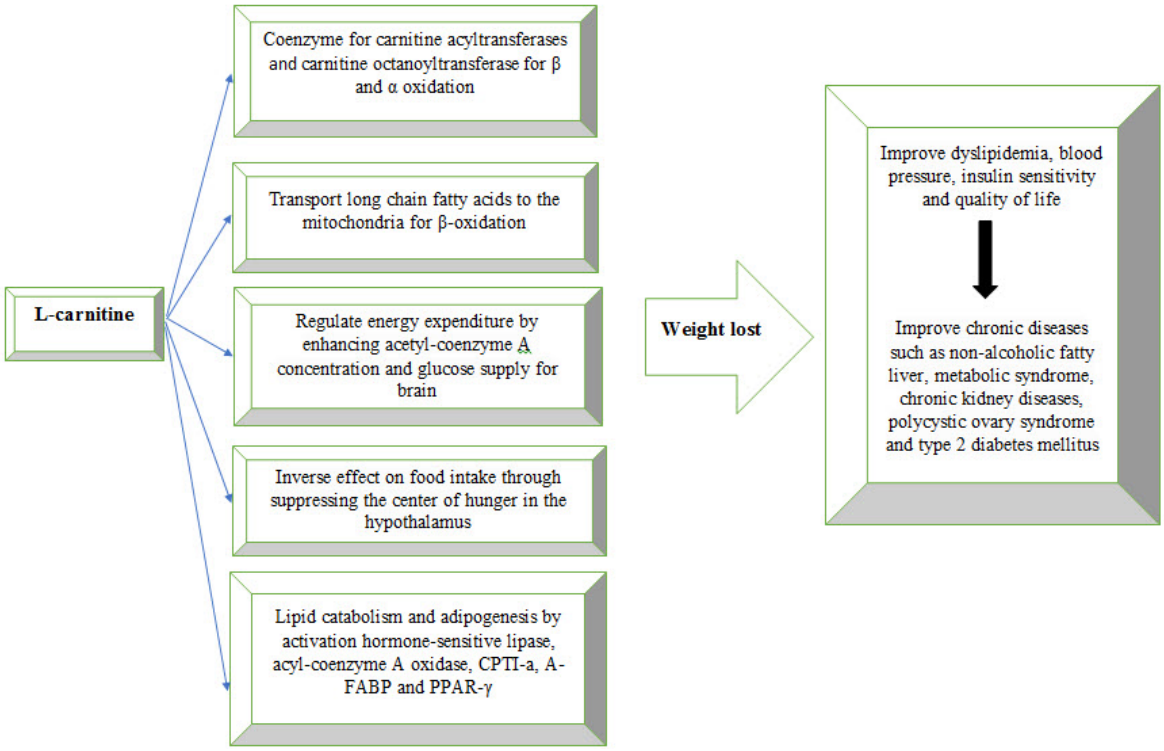

Fig. 5. Mechanisms of L-carnitine in weight lost and improving chronic diseases. CPTI-a, carnitine palmitoyltransferase I-a; A-FABP, adipose-specific fatty acid-binding protein; PPAR-γ, peroxisome proliferator-activated receptor-gamma.

for the increased incidence of atherosclerosis [58,59]. Our study findings supported the efficacy of a daily dosage of >1000 mg and demonstrated adequacy in achieving the desired effects. However, for minimizing the incidence of the aforementioned side effects, consuming high doses for longer durations should be done with caution.

5. Strengths and Limitations

To the best of our knowledge, the present study is the first umbrella meta-analysis investigating the effects of L-carnitine supplementation on weight, BMI, and WC. All of the included meta-analyses studies in this umbrella review had high quality. Nevertheless, there were some limitations. Due to the nature of this study, the primary studies included in the selected meta-analyses were not assessed in detail, while some of them were included in meta-analyses several times. This could introduce a potential source of bias, therefore, this limitation should be considered in the interpretation of the results. As previously mentioned, RCTs incorporating co-treatment alongside L-carnitine have been included in a meta-analysis [11], potentially influencing the outcomes, which were amended through sensitivity analysis. Additionally, due to high heterogeneity across the studies, subgroup analysis was implemented to identify the source of heterogeneity.

6. Conclusion

The results from the present umbrella meta-analysis supports L-carnitine supplementation in the management of obesity. According to the evidence, it seems that favorable impacts are achieved with dosages >1000 mg/day and supplementation duration <18 weeks.

Author Contributions

FH, MM, and MZ designed the research and wrote the manuscript. ParsJ and ParmJ, RM conducted the systematic search. FH screened the articles and extracted the data. MZ and AO analyzed and interpreted the data. ParsJ and ParmJ drew the tables. FH and MZ had primary responsibility for the final content. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The protocol of this study was approved and supported by the Student Research Committee, Tabriz University of Medical Sciences (69438).

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/IJVNR40033.

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