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REVIEW ARTICLE

The effects of L-carnitine supplementation on indicators of inflammation and oxidative stress: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Objective Several trials investigated the efficacy of L-carnitine administration on markers of inflammation and indicators of oxidative stress; however, their findings are controversial. The aim of this study was to conduct a comprehensive meta-analysis and a critical review, which would analyze all randomized controlled trials (RCTs) in order to determine the effects of L-carnitine supplementation on inflammatory markers and oxidative stress.

Methods An electronic search was performed using Scopus, Cochrane Library, PubMed, Google scholar and Web of Science databases on publications from 1990 up to May 2020. Human RCTs conducted in healthy subjects or participants with certain disorders which investigating the efficacy of L-carnitine supplementation compared to control (placebo, usual treatment or no intervention) on inflammation and oxidative markers were included. Data were pooled applying a random-effects model and as the overall effect size, weighted mean difference (WMD) was presented. Between heterogeneity among studies was computed using Cochran's Q test and I-square (I^2). Quality of studies assessed using the Jadad scale. Dose-response analysis was measured using meta-regression. The funnel plot, as well as the Egger's regression test was applied to determine the publication bias.

Results 44 trials (reported 49 effect sizes for different outcomes of interest) met the inclusion criteria for this meta-analysis. According to the findings, L-carnitine supplementation resulted in a significant reduction in C-reactive protein (CRP) (WMD: -0.10; 95% CI: -0.14, -0.06), interleukin 6 (IL-6) (WMD: -1.87; 95% CI: -2.80, -0.95), tumor necrosis factor-α (TNF-α) levels (WMD: -1.43; 95% CI: -2.03, -0.84), and malondialdehyde (MDA) (WMD: -0.47; 95% CI: -0.76, -0.18) levels, while there was a significant increase in superoxide dismutase (SOD) (WMD: 2.14; 95% CI: 1.02, 3.25). However, no significant effects of L-carnitine on glutathione peroxidase (GPx) (WMD: 0.02; 95% CI: -0.01, 0.05) and total antioxidant capacity (TAC) (WMD: 0.14; 95% CI: -0.05, 0.33) were found.

Conclusions L-carnitine supplementation was associated with lowering of CRP, IL-6, TNF-α, and MDA, and increasing SOD levels, but did not affect other inflammatory and oxidative stress biomarkers.

Keywords Carnitine · Inflammatory markers · C-reactive protein · Oxidative stress · Meta-analysis

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Introduction

Inflammation is a complex biological process related to infection, irritation etc. [1]. During chronic inflammation and oxidative stress, there is an elevated levels of free radicals and reactive oxygen species (ROS), which may cause structural damage to the cells [2]. Inflammation and oxidative stress are associated with a wide range of chronic diseases including atherosclerosis, diabetes mellitus (DM), neurological disorders, pulmonary diseases, cancer, and rheumatoid arthritis (RA) [3].

Carnitine is effective in preventing accumulation of end-products related to lipid peroxidation due to its anti-inflammatory and antioxidant effects [4]. The major physiologic role of carnitine is transferrin of long-chain fatty acids through the mitochondrial membrane and contribution in the oxidative release of energy [5]. It also helps to remove the short- and medium-chain fatty acids from mitochondria [6]. Any change in carnitine homeostasis may have an impact on metabolism and function of lipids, red blood cells, and cardiac muscle cells [7]. The influences of carnitine supplementation on many biomarkers of inflammation and oxidative stress have already been investigated, but the findings were not conclusive. In a meta-analysis by Sahebkar et al. [8], a beneficial effect of carnitine supplementation in decreasing circulating levels of C-reactive protein (CRP) were found. Carnitine supplementation at a dosage of 20 mg/kg of body weight during 8 weeks to patients with end-stage renal disease was attributed to a significant decrease in biomarkers of oxidative stress [9]. Moreover, it has been suggested that carnitine administration at a dosage of 1.5 g/day during 2 months to patients with maple syrup urine disease (MSUD) has an antioxidant and anti-inflammatory effect [10]. Taking carnitine supplements during 3 months by patients with age-related macular degeneration (AMD) significantly reduced oxidative damage by reducing a marker of lipid peroxidation malondialdehyde (MDA) and increasing glutathione (GSH) levels [11]. However, Shakeri et al. [12] did not find any favorable effects of carnitine supplementation during 12 weeks on parameters of oxidative stress in hemodialysis subjects with hyperlipoproteinemia. Furthermore, Sawicka et al. [13] indicated that 1,500 mg/day carnitine supplementation for 24 weeks to healthy women older than 65 years had no effects inflammatory variables.

Discrepancies among existed evidence might be related to the differences in several factors such as study design, characteristics of studies populations, comorbidities, duration of intervention, as well as different formulations and dosages of carnitine used. Therefore, we performed this meta-analysis to identify the effect of L-carnitine on inflammation and oxidative stress.

Methods

Search strategy

Two independent authors searched electronic databases including Scopus, Cochrane Library, Web of Science, PubMed and Google scholar databases from 1990 to May 2020 for relevant randomized controlled trials (RCTs) investigating the associations between L-carnitine supplementation and indicators of oxidative stress and inflammatory profiles. Search strategy was limited to RCTs in humans with written in English or Persian. The following keywords were used to identify primary articles: intervention ("L-carnitine" OR "L-carnitine -L-tartrate" OR "propionyl L-Carnitine" OR "Acetyl-L-carnitine" OR "carnitine orotate complex"), and outcomes ["tumor necrosis factor-α (TNF-α)" OR "C-reactive protein (CRP)" OR "interleukin 6 (IL-6)" OR "total antioxidant capacity (TAC)" OR "malondialdehyde (MDA)" OR "glutathione peroxidase (GPx)" OR "Superoxide dismutase (SOD)"]. In order to detect further articles that were not captured in our primary search, we searched the reference lists of related RCTs and previous reviews manually.

Inclusion and exclusion criteria

For this meta-analysis, we included RCTs, which fulfilled the following criteria: (1) Participants: healthy subjects or individuals with different underlying conditions and disorders. (2) Intervention: oral or intravenous carnitine supplementation for a duration more than 2 weeks. (3) Comparisons: control (placebo, usual treatment or no intervention). (4) Outcomes: inflammatory biomarkers and indicators of oxidative stress. (5) Study design: parallel design or cross-over. Due to the unfamiliarity with other languages, relevant articles which were written English or Persian were included. Data were extracted from RCTs presented mean/median with standard deviation (SD) or standard error or interquartile range or related 95% confidence intervals (CIs) for the both intervention and control groups. Other studies such as *in vitro* studies, animal model investigations, case reports and observational studies were excluded. In addition, investigations with healthy control (case control studies) or without control group and trials with two weeks or less duration were not included.

Data extraction and quality assessment

Two authors (HF and AM) independently screened the articles based on the eligibility criteria. In the first step the title and abstract of studies were reviewed. Then, the full-text of relevant studies was assessed to ascertain the suitability of a study for including in the meta-analysis. Any disagreement was resolved by the judgment of the concealment of third author (JH).

The following data were extracted from selected studies: the name of first authors, publication year, study location, study design, sample size, age, health status and type of disease, duration of the intervention, dosage of supplementation, the mean and SD for biomarkers of inflammation and oxidative stress in each intervention group. The same two authors also assessed the studies' quality independently using the Jada tool.

Data synthesis and statistical analysis

The pooled effects of L-carnitine supplementation on the each indicator of inflammation and oxidative stress were calculated applying change score method. Weighted mean difference (WMD) with related 95% CI was used for pooling data to determine the overall effect sizes by using the random-effect model.

Heterogeneity and publication bias

Using Cochran's Q test (with significant P-value < 0.1) and I-square test (I^2 greater than 50 percent showing significant heterogeneity) heterogeneity across included trials was evaluated. We conducted different subgroup analyses to reveal potential sources of between-study heterogeneity. These subgroup analyses were done based on participants' age, health condition of participants, study location, dosage of supplements, study duration, and sample size. In order to determine the publication bias, funnel plot, as well as the test of Egger's regression was used. For data analysis, both STATA 11.0 (Stata Corp., College Station, TX) and Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) software were applied.

Results

Following an initial search in mentioned databases, 5671 articles were recognized. Among them, 5147 articles were duplicates, review, case report, not RCT and not human studies and then removed. Then, 524 articles were screened based on title and abstract. After screening, 458 publication were excluded due to non-relevant studies. Then, 66 articles were eligible to evaluate their full-text. Of these, 22 articles were excluded due to duration equal or below 2 weeks (n = 14), Non-randomized design (n = 03), healthy control or not having control group (n = 03), outcome assessment with non-desired methods (n = 01), not having end of trial data (n = 01). Finally, 44 articles were included to present systematic review and meta-analysis. Flowchart of procedure for study selectin is presented in Fig. 1.

In Table 1, general characteristics of included studies are given. In total, 44 studies which reported 49 effect sizes were included with a total of 2742 subjects (1429 subjects in intervention and 1313 subjects in control groups). These studies were published between 2000 and 2019 and were conducted in Turkey, India, Italy, USA, Japan, Iran, Greece, Egypt, Taiwan, Spain, Malaysia, Poland, and Korea. The duration of supplementation varied between 4 and 48 weeks. L-carnitine, carnitine orotate complex, propionyl L-carnitine, Glycine propionyl-L-carnitine, Acetyl-L-carnitine, and L-carnitine -L-tartrate were used as supplements in the included studies; one study used L-carnitine enriched bread and one another a fruit-flavored drink. Thirty two studies were at a quality score ≥ 3 and 12 others had a quality score < 3 (Table 4).

Ten studies used a carnitine dosage < 500 mg [9, 15–17, 21, 34, 35, 38, 48, 52]. In seven trials [22, 32, 36, 39, 41, 45, 47] and one effect size [23] (a) a dosage ≥ 500–1000 mg was administrated. A dosage ≥ 1000–2000 mg was provided in 12 studies [12, 19, 20, 26, 27, 31, 42, 43, 46, 50, 53, 54] and one effect size [25] (a). A dosage ≥ 2000 mg was reported in 13 studies [14, 18, 24, 28–30, 33, 37, 40, 44, 49, 51, 55], and 2 effect sizes [23] (b) and [25] (b).

Based on the most included studies, carnitine supplementation was well tolerated and no significant side effects were observed in the intervention compared to the control groups [9, 14, 16, 22–24, 26, 28–30, 32–35, 39, 41–46, 48, 49, 51, 52, 54, 55]. In 2 studies the reason of withdrawal in the carnitine group were as follow: diarrhea which resolved after gastroenterology concealment and halving the intervention dosage for 1 week [21] and pruritic rash and nausea which were resolved after discontinuation of study intervention [19]. However, 15 studies did not mention or assess the adverse effects related to carnitine supplementation [12, 15, 17, 18, 20, 25, 27, 31, 36–38, 40, 47, 50, 53].

The effects of L-carnitine administration on inflammatory cytokines

A pooled analysis of 30 effect sizes revealed that following L-carnitine supplementation significant reduction in CRP concentrations was achieved (WMD: -0.10; 95% CI: -0.14, -0.06) (Fig. 2A and Table 2). This finding did not remain significant in studies performed in patients aged ≥ 65 years (WMD: 0.01; 95% CI: -0.00, 0.02), Western countries (WMD: -0.02; 95% CI: -0.04, -0.00), patients with renal disease (WMD: -0.03; 95% CI: -0.06, -0.00), or liver diseases (WMD: -0.00; 95% CI: -0.02, 0.01), and cancer disease (WMD: -0.18 95% CI: -0.42, 0.06), studies which used dosages of 500–1000 mg/day (WMD: -0.01; 95% CI: -0.02, 0.01), those with a duration of 6–12 months (WMD: 0.00; 95% CI:

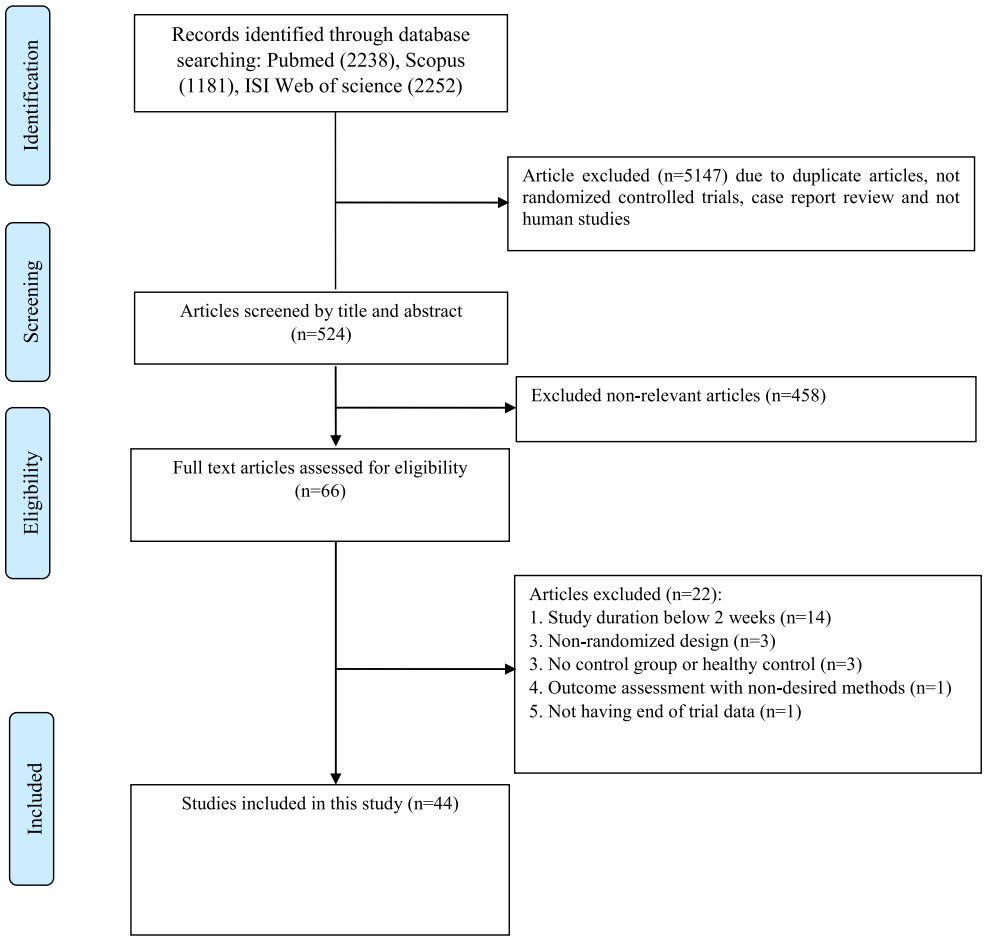


Fig. 1 Literature search and review flowchart for selection of studies

-0.03, 0.04), and studies with a sample size of < 50 (WMD: 0.01; 95% CI: -0.00, 0.02). Carnitine supplementation increased CRP levels in healthy individuals (WMD: 0.02; 95% CI: 0.01, 0.04) and studies which used dosages of < 500 mg/day (WMD: 0.06; 95% CI: 0.03, 0.09) (Table 3).

L-carnitine also reduced IL-6 levels, as shown in the meta-analysis of 13 effect sizes (WMD: -1.87; 95% CI: -2.80, -0.95) (Fig. 2B and Table 2). This finding did not change in our subgroup analyses, except for studies done in Western countries (WMD: -0.06; 95% CI: -0.28, 0.17), studies with a duration of 6–12 months (WMD: -0.14; 95% CI: -0.39, 0.11), studies with a sample size of < 50 (WMD: -0.09; 95% CI: -0.33, 0.15), and those done on healthy subjects (WMD: -0.08; 95% CI: -0.32, 0.15) or patients with renal disease (-3.20, 95%CI -7.46, 1.06 (Table 3).

Pooling findings of 13 studies showed a significant reduction in TNF-α concentrations (WMD: -1.43; 95% CI: -2.03, -0.84) (Fig. 2C and Table 2) which did not alter in all subgroup analyses (Table 3). Moreover, after excluding one study (Maccio et al.) which had greatly different results from the other studies, overall finding did not change (WMD: -0.73; 95% CI: -1.14, -0.31).

The effects of L-carnitine on antioxidant enzymes

L-carnitine supplementation had no significant on the levels of GPx enzyme (WMD: 0.02; 95% CI: -0.01, 0.05) (Fig. 2D and Table 2). However, a significant elevation of GPx levels following L-carnitine supplementation was seen in subgroup analysis based on study location (Table 3). L-carnitine supplementation significantly increased the levels of SOD enzyme in the pooled analysis (WMD: 2.14; 95% CI: 1.02, 3.25) (Fig. 2E and Table 2) and in all subgroup analyses (Table 3).

The effects of L-carnitine on endogenous antioxidants

After combining 9 effect sizes, no significant effect of L-carnitine supplementation on TAC enzyme levels was found (WMD: 0.14; 95% CI: -0.05, 0.33) (Fig. 2F and Table 2). A significant increase in TAC levels was seen after subgroup analysis based on study location. Such an increase was also found in studies with a sample size of < 50 (WMD: 0.29; 95% CI: 0.25, 0.33) and studies used a dosage < 500 mg/day (WMD: 0.50; 95% CI: 0.44, 0.56) (Table 3).

Table 1 Summary of included randomized controlled studies

Authors (Ref)	Publication year	Country	Sample size (intervention/control)	Duration (wk)	Age (y) (intervention/control)	Intervention (type and dosage)	Total quality score
Gurlek et al.[14]	2000	Turkey	31/20	4	64.3 ± 7.8, 66.2 ± 8.7	2000 mg L-carnitine	2
Vesela et al.[15]	2001	Germany	12/12	24	28–71	15 mg/kg L-carnitine three times/week	1
Mosca et al.[16]	2002	Italy	9/6	16	29–40	100 mg N-acetl-L-carnitine + 100 mg L-carnitine + selenomethionin + αtocopherol + Q10 + α lipoic acid	2
Duranay et al.[17]	2006	Turkey	21/21	24	44.0 ± 13.9, 43.4 ± 13.9	20 mg/kg L-carnitine three times/week	3
Kumar et al.[18]	2007	India	29/29	12	52.9 ± 6.4, 50.4 ± 7.7	2250 mg L-carnitine + 270 mg ubiquinol	5
McMackin et al.[19]	2007	USA	36/26	8	≥ 55	1000 mg acetyl-L-carnitine + 200 mg α-lipoic acid	5
Yonei et al.[20]	2007	Japan	18/17	8	40–69	1000 mg L-carnitine + 700 mg conjugated linoleic acid	3
Ates et al.[21]	2008	Turkey	30/30	12	55–70	200 mg L-carnitine	2
Yonei et al.[22]	2008	Japan	18/17	8	48.3 ± 6.9	600 mg L-carnitine + 500 mg Garcinia cambogia extract	3
Bloomer et al.[23] (a)	2009	USA	10/4	8	18–44	1000 mg GPLC + aerobic exercise	4
Bloomer et al.[23] (b)	2009	USA	11/5	8	18–44	3000 mg GPLC + aerobic exercise	4
Bloomer et al.[24]	2009	USA	14/15	8	20–55	3000 mg acetyl L-carnitine arginate	4
Bloomer et al.[25] (a)	2009	USA	11/4	8	20–40	1000 mg propionyl L-carnitine + 348 mg glycine + aerobic exercise	4
Bloomer et al.[25] (b)	2009	USA	12/5	8	20–40	3000 mg propionyl L-carnitine + 1044 mg glycine + aerobic exercise	4
Derosa et al.[26]	2011	Italy	114/113	48	51 ± 4, 53 ± 6	2000 mg + 360 mg orlistat	5
Hakeshzadeh et al.[27]	2010	Iran	18/18	12	20–74	1000 mg L-carnitine	3
Malaguarnera et al.[28]	2010	Italy	36/38	24	47.9 ± 5.4, 47.8 ± 5.8	2000 mg L-carnitine + diet	5
Mantovani et al.[29]	2010	Italy	88/44	16	62.4 ± 9.4, 61.5 ± 9.7	4000 mg L-carnitine + a prostagelandin agent + EPA + thalidomide	2
Shakeri et al.[12]	2010	Iran	18/18	12	24–80	1000 mg L-carnitine	2
Fatouros et al.[9]	2010	Greece	12/12	8	53.8 ± 7.96	20 mg/kg L-carnitine three times/week	4
Derosa et al.[30]	2010	Italy	113/110	12	≥ 18	2000 mg L-carnitine + 10 mg sibutramine	5
Suchitra et al.[31]	2011	India	20/15	24	50.2 ± 8.6, 53.4 ± 9.6	1000 mg L-carnitine three times a week	3
Mortazavi et al.[32]	2011	Iran	24/24	36	50.66 ± 17, 57.91 ± 13	750 mg L-carnitine	5
Macciò et al.[33]	2012	Italy	61/63	24	35–76	4000 mg L-carnitine + megestrol acetate + celecoxib + antioxidants	2

Table 1 (continued)

Authors (Ref)	Publication year	Country	Sample size (intervention/control)	Duration (wk)	Age (y) (intervention/control)	Intervention (type and dosage)	Total quality score
Karl et al.[34] (a)	2012	USA	21/7	8	58 ± 15, 63 ± 9	fruit-flavored drink containig 300 mg L -carnitine + other nutrients	4
Karl et al.[34] (b)	2012	USA	23/7	8	60 ± 13, 63 ± 9	fruit-flavored drink containig 300 mg L -carnitine + other nutrients + red yeast rice	4
Rondanelli et al.[35]	2013	Italy	41/45	8	25–45	300 mg L-carnitine + botanical extracts	4
Fukami et al.[36]	2013	Japan	32/38	24	68.±12.4, 67 ± 13.2	900 mg L-carnitine	2
Barzegar et al.[37]	2013	Iran	30/30	8	20–50	2000 mg L-carnitine + low-calorie diet	2
Higuchi et al.[38]	2014	Japan	67/64	48	20–85	20 mg/kg L-carnitine	2
Hong et al.[39]	2014	Korea	24/24	12	30–75	900 mg carnitine orotate complex + metformin	3
Samadi et al.[40]	2014	Iran	9/11	8	20–30	2000 mg L-carnitine	4
Soare et al.[41]	2014	USA	28/26	12	38–55	500 mg acetyl-L-carnitine + other nutrients	4
Lee et al.[42]	2014	Taiwan	20/19	12	71.9 ± 10.6, 72.7 ± 10.1	1000 mg L-carnitine	3
Lee et al.[43]	2015	Taiwan	20/19	12	71.9 ± 10.6, 72.7 ± 10.1	1000 mg L-carnitine	3
Bañuls et al.[44] (a)	2015	Spain	15/13	12	51.7 ± 7.7	2325 mg L-carnitine enriched bread + soluble fiber	4
Bañuls et al.[44] (b)	2015	Spain	11/15	12	53.8 ± 10.7	2325 mg L-carnitine enriched bread + soluble fiber	4
Malek Mahdavi et al.[45]	2015	Iran	33/36	8	40–60	750 mg L-carnitine	5
Badrasawi et al.[46]	2016	Malaysia	26/24	10	68.2 ± 6.3, 68.8 ± 6.5	1500 mg L-carnitine	5
Malek Mahdavi et al.[47]	2016	Iran	33/36	8	40–60	750 mg L-carnitine	5
Jamilian et al.[48]	2017	Iran	30/30	12	18–40	250 mg carnitine	5
Mohammadi et al.[49]	2017	Iran	26/26	8	41.0 ± 9.65, 40.6 ± 9.90	2000 mg L-carnitine tartrate	4
Sharifi et al.[50] (a)	2017	Iran	32/31	12	40–65	1200 mg L-carnitine + 150 mg Q10	3
Sharifi et al.[50] (b)	2017	Iran	32/32	12	40–65	1200 mg L-carnitine + 150 mg Q10 + TLC diet	3
Koozehchian et al.[51]	2018	Iran	12/11	9	25.5 ± 1.5, 24.5 ± 1.5	2000 mg L-carnitine	4
Talari et al.[52]	2019	Iran	30/30	12	18–40	250 mg carnitine	5
Samulak et al.[53]	2019	Poland	11/9	24	65–70	1500 mg L-carnitine-L-tartrate	1
Jamilian et al.[54]	2019	Iran	26/27	12	18–40	1000 mg L-carnitine + 200 μg chromium	5
El-Sheikh et al.[55]	2019	Egypt	31/27	24	≥30	2000 mg L-carnitine + glimepiride	2

Y, Year; EPA, eicosapentaenoic acid; GPLC, Glycine propionyl-L-carnitine.

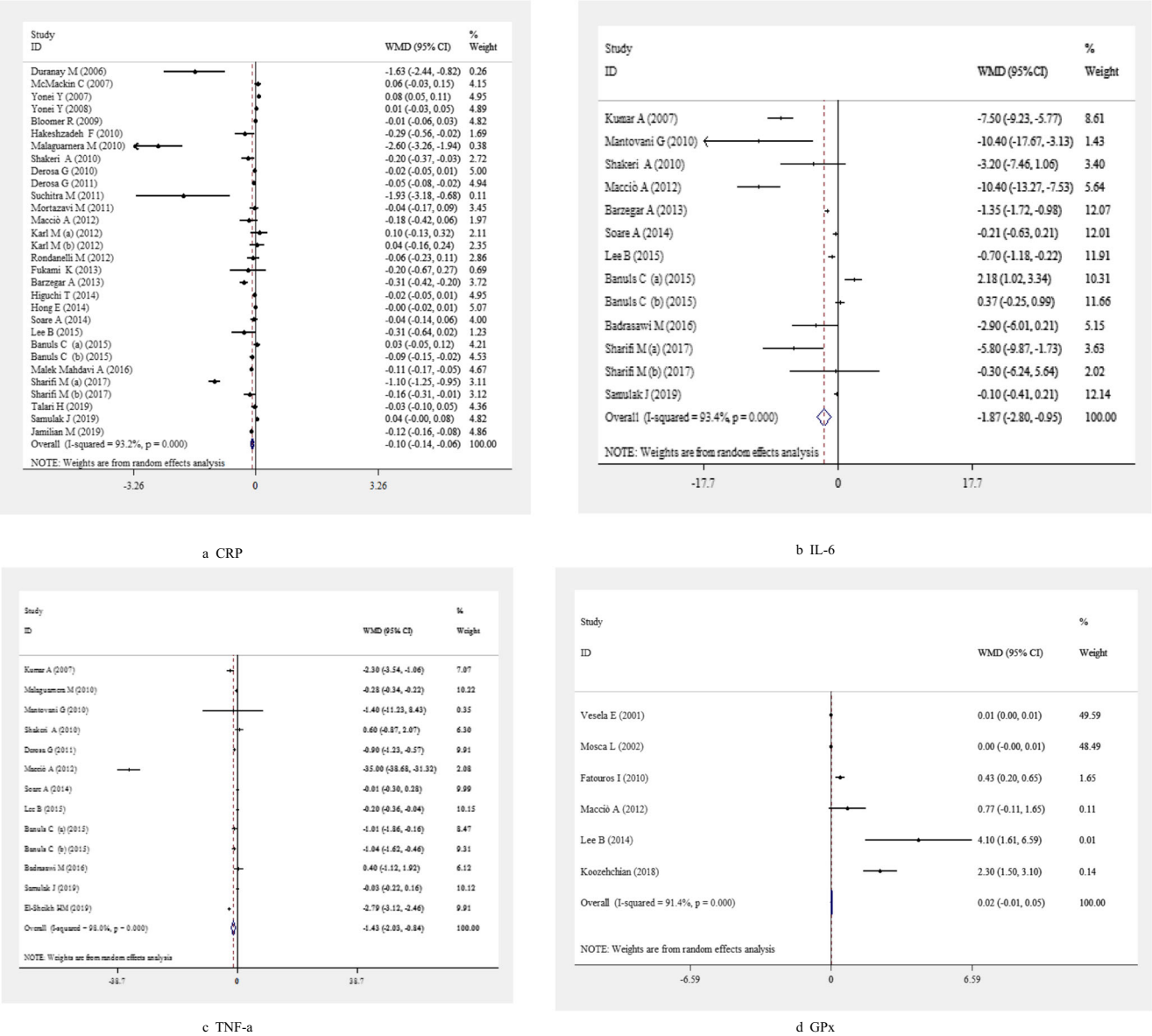


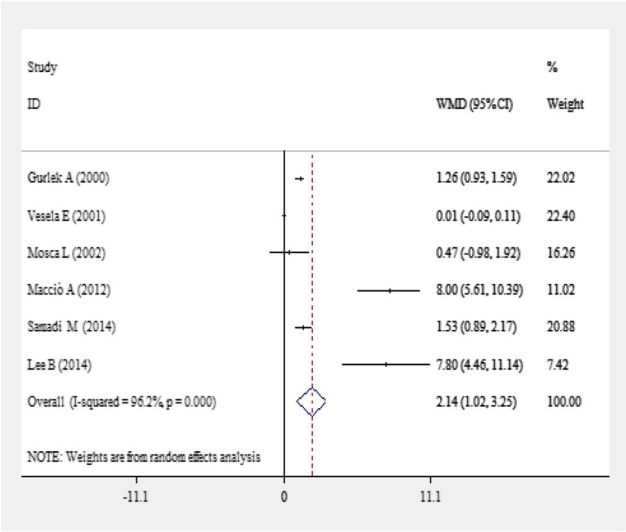
Fig. 2 Meta-analysis biomarkers of inflammation and oxidative stress weighted mean difference estimates for **A**) CRP, **B**) IL-6, **C**) TNF-α, **D**) GPx, **E**) SOD, **F**) TAC, **G**) MDA in the L-carnitine supplements and placebo groups (CI=95%)

The effects of L-carnitine administration on other biomarkers of oxidative stress

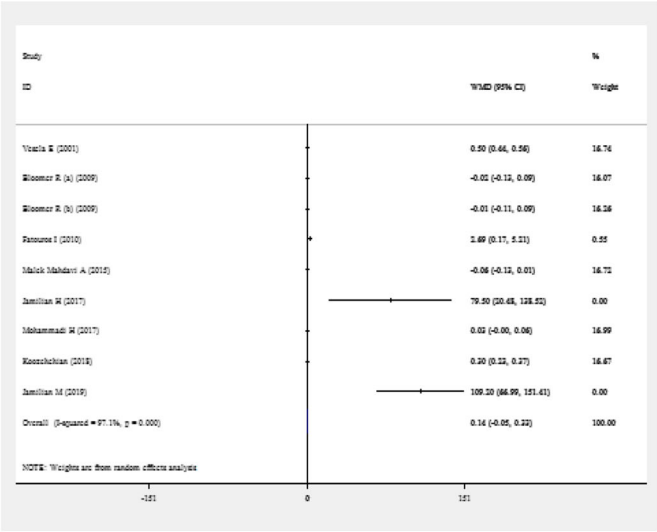
L-carnitine supplementation was associated with a significant decrease in MDA (WMD: -0.47; 95% CI: -0.76 -0.18) (Fig. 2G and Table 2). Findings of subgroup analyses were similar to the pooled analyses. However, L-carnitine supplementation did not alter MDA levels in studies which used L-carnitine supplements at daily dosages more than 2000 mg/day (WMD: -0.04; 95% CI: -0.08, 0.01) (Tables 3 and 4).

Meta-regression

Meta-regression showed A significant inverse association between carnitine supplementation dosage and serum levels of TNF-α (P = 0.02) and IL-6 (P = 0.01). However, no



e SOD



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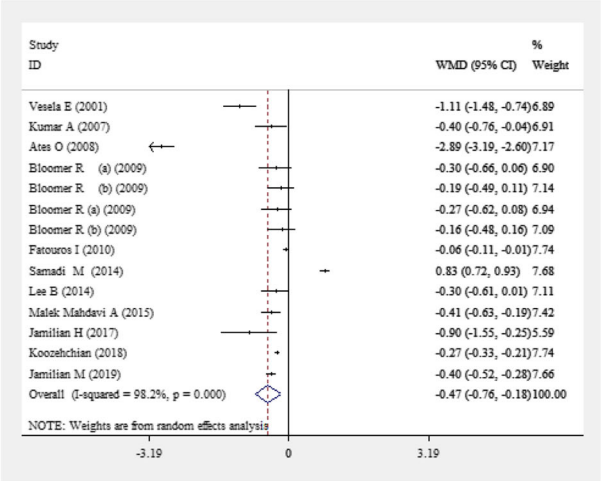


g MDA

Fig. 2 continued.

Table 2 The effects of L-carnitine supplementation on biomarkers of inflammation and oxidative stress

Variables	Number of effect sizes	Weighted mean difference	CI 95%	Heterogeneity	
				I^2 (%)	P- value heterogeneity
CRP	30	-0.10	-0.14, -0.06	93.2	< 0.001
IL-6	13	-1.87	-2.80, -0.95	93.4	< 0.001
TNF-α	13	-1.43	-2.03, -0.84	98.0	< 0.001
GPx	6	0.02	-0.01, 0.05	91.4	< 0.001
SOD	6	2.14	1.02, 3.25	96.2	< 0.001
TAC	9	0.14	-0.05, 0.33	97.1	< 0.001
MDA	14	-0.47	-0.76, -0.18	98.2	< 0.001

CRP: C-reactive protein; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-α; GPx: Glutathione Peroxidase; SOD: Superoxide dismutase; TAC: Total Antioxidant Capacity; MDA: Malondialdehyde

Table 3 Subgroup analyses for the effects of L-carnitine supplementation on biomarkers of inflammation and oxidative stress

Variables		Subgroups	Number of effect sizes	Pooled WMD	95% CI	I^2 (%)	Between-study I^2 (%)
CRP	Participants' age	< 45 year	6	-0.05	-0.07, -0.03	84.0	< 0.001
		45–65 year	14	-0.06	-0.04, -0.02	95.7	
		≥ 65 years	10	0.01	-0.00, 0.02	80.3	
	Country	Eastern	16	-0.02	-0.03, -0.01	95.4	< 0.001
		Western	14	-0.02	-0.04, -0.00	86.4	
	Health condition	Healthy	9	0.02	0.01, 0.04	72.4	< 0.001
		Renal disease	7	-0.03	-0.06, -0.00	81.1	
		CVD	4	-0.23	-0.30, -0.16	98.3	
		Chronic metabolic diseases	6	-0.05	-0.07, -0.03	87.6	
		Liver diseases	2	-0.00	-0.02, 0.01	98.3	
		Cancers	1	-0.18	-0.42, 0.06	-	
		Other diseases	1	-0.11	-0.17, -0.05	-	
	Administration dosage	< 500 mg	4	0.06	0.03, 0.09	53.3	< 0.001
		500–1000 mg	7	-0.01	-0.02, 0.01	78.5	
		1000–2000 mg	11	-0.06	-0.09, -0.04	96.6	
		≥ 2000 mg	8	-0.04	-0.06, -0.02	92.1	
	Study duration	< 6 month	21	-0.02	-0.03, -0.01	94.2	0.09
		6–12 month	7	0.00	-0.03, 0.04	93.2	
		≥ 12 month	2	-0.03	-0.06, -0.01	37.6	
	Sample size	< 50	16	0.01	-0.00, 0.02	79.8	< 0.001
		50–100	9	-0.15	-0.17, -0.12	96.6	
		≥ 100	5	-0.03	-0.05, -0.01	8.5	
IL-6	Participants' age	< 65 year	8	-0.69	-0.93-0.44	94.4	0.10
		≥ 65 years	5	-0.39	-0.65, -0.13	92.8	
	Country	Eastern	7	-1.33	-1.62, -1.04	90.3	< 0.001
		Western	6	-0.06	-0.28, 0.17	93.3	
	Study duration	< 6 month	11	-0.96	-1.22, -0.71	93.8	< 0.001
		6–12 month	2	-0.14	-0.39, 0.11	00.0	
	Sample size	< 50	5	-0.09	-0.33, 0.15	84.0	< 0.001
		50–100	6	-1.05	-1.32, -0.78	93.6	
		≥ 100	2	-10.40	-13.07, -7.73	00.0	
	Health condition	Healthy	4	-0.08	-0.32, 0.15	46.0	< 0.001
		Renal disease	1	-3.20	-7.46, 1.06	-	
		CVD	4	-1.25	-1.71, -0.79	95.0	
		Chronic metabolic diseases	2	-1.02	-1.38, -0.67	96.9	
		Cancers	2	-10.40	-13.07, -7.73	00.0	
TNF-α	Country	Eastern	4	-0.22	-0.38,-0.06	76.3	0.12
		Western	9	-0.35	-0.40, -0.30	98.6	
	Sample size	< 50	5	-0.18	-0.30, -0.06	74.3	< 0.001
		50–100	5	-0.35	-0.41, -0.29	98.2	
		≥ 100	3	-1.17	-1.50, -0.84	99.4	
GPx	Country	Eastern	2	2.47	1.71, 3.23	45.1	< 0.001
		Western	4	0.01	0.00, 0.01	81.6	
SOD	Participants' age	< 65 year	2	1.36	0.77, 1.94	41.7	< 0.001
		≥ 65 year	4	0.13	0.03, 0.22	97.4	
	Country	Eastern	2	1.75	1.12, 2.38	92.3	< 0.001
		Western	4	0.12	0.03, 0.22	96.8	
TAC	Country	Eastern	5	0.05	0.02, 0.08	95.8	< 0.001
		Western	4	0.29	0.24, 0.34	97.2	
	Sample size	< 50	5	0.29	0.25, 0.33	96.3	< 0.001
		≥ 50	4	0.01	-0.01, 0.04	84.3	

Table 3 (continued)

Variables		Subgroups	Number of effect sizes	Pooled WMD	95% CI	I^2 (%)	Between-study I^2 (%)
		< 500 mg	2	0.50	0.44, 0.56	85.5	< 0.001
		500–1000 mg	2	-0.06	-0.12, 0.01	78.1	
		1000–2000 mg	2	-0.02	-0.13, 0.10	96.1	
		≥ 2000 mg	3	0.06	0.04, 0.09	96.1	
MDA	Participants' age	< 45 year	8	-0.10	-0.14, -0.05	98.1	< 0.001
		45–65 year	3	-0.08	-0.13, -0.03	83.5	
		≥ 65 years	3	-1.53	-1.71, -1.34	98.6	
	Country	Eastern	7	-0.11	-0.15, -0.07	98.4	< 0.09
		Western	7	-0.16	-0.21, -0.12	98.4	
	Administration dosage	< 500 mg	3	-2.04	-2.26, -1.83	97.1	< 0.001
		500–1000 mg	2	-0.08	-0.13, -0.03	89.1	
		1000–2000 mg	4	-0.37	-0.47, -0.27	00.0	
		≥ 2000 mg	5	-0.04	-0.08, 0.01	98.8	
	Sample size	< 50	9	-0.06	-0.10, -0.03	97.8	< 0.001
		≥ 50	5	-0.66	-0.75, -0.56	98.4	

CRP: C-reactive protein; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-α; GPx: Glutathione Peroxidase; SOD: Superoxide dismutase; TAC: Total Antioxidant Capacity; MDA: Malondialdehyde

significant association was found between supplementation dosage and serum CRP (P = 0.70), TAC (P = 0.36) and MDA (P = 0.05) concentrations.

Publication bias

No evidence of publication bias among the included studies was showed in visual inspection of funnel plots for CRP, IL-6, TNF-α, TAC and MDA (Fig. 3A-E).

Discussion

In this meta-analysis, we investigated the effects of L-carnitine supplementation on the biomarkers of inflammation and oxidative stress. Our findings demonstrated that L-carnitine supplementation significantly attenuated CRP, IL-6, TNF-α, and MDA, and increased SOD levels, but did not influence GPx and TAC levels. Also dose-response meta-regression showed a significant inverse association between carnitine supplementation dosage and serum IL-6 and TNF-α concentrations which means reduction in the concentrations of these inflammatory cytokines following carnitine supplementation was more expressed in studies with higher dosage.

Effects on inflammatory profiles

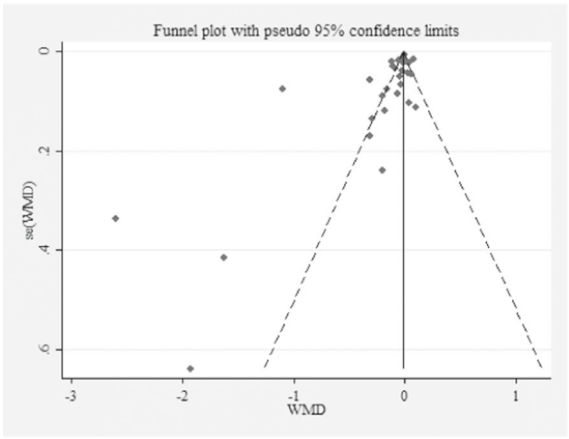
In this meta-analysis, we showed that L-carnitine supplementation significantly lowerd the levels of CRP, IL-6 and TNF-α. In line with our findings, a meta-analysis on 13 trials indicated that oral carnitine supplementation led to decrease in the levels inflammatory variables in subjects with diverse underlying conditions [56]. Similarly, another meta-analysis performed by Sahebkar et al. [8] indicated that oral L-carnitine supplementation was associated with a significant decrease in CRP levels. In addition, another meta-analysis showed that carnitine administration in hemodialysis patients significantly reduced CRP values [57]. However, in some studies carnitine consumption was not effective for the attenuation of inflammation. For example, Sawicka et al. [13] failed to show any significant effects of carnitine supplementation at a dosage of 1,500 mg/day for 24 weeks on IL-6, TNF-α and CRP concentrations in healthy women older than 65 years. In another study, the consumption of carnitine-enriched bread foe three months did not change circulating inflammatory markers among participants with or without metabolic syndrome (MetS), which is opposite to our findings [44]. It is evidenced that elevated inflammatory status contributes to development and progression of atherosclerosis and cardiovascular disease [58]. In addition, higher CRP level is associated with increased mortality in general population and some chronic disorders [59–61]. Anti-inflammatory interventions may provide beneficial effects for targeting atherosclerosis [62]. Carnitine may play several important roles in the amelioration of inflammation, It is well known that ROS are as enhancers of inflammatory environment [63]. Therefore, the role of carnitine in decreasing inflammatory response, in part can be explained by its ability to reducing of ROS production [64]. Carnitine also exert a significant anti-inflammatory role through downregulation of nuclear factor kappa B pathway which leads to decrease in the expression of pro-inflammatory cytokines [65].

Table 4 Methodological quality scores for included studies using Jadad scale

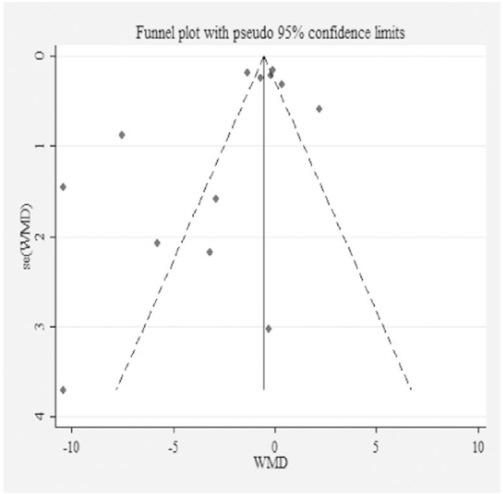
Study	Randomization	Blinding	Account of all patients	Total Score
Gurlek et al.2000	1	0	1	2
Vesela et al.2001	0	0	1	1
Mosca et al.2002	1	0	1	2
Duranay et al.2006	2	0	1	3
Kumar et al.2007	2	2	1	5
McMackin et al.2007	2	2	1	5
Yonei et al.2007	1	1	1	3
Ates et al.2008	1	0	1	2
Yonei et al.2008	1	1	1	3
Bloomer et al.2009	1	2	1	4
Bloomer et al.2009	1	2	1	4
Bloomer et al.2009	1	2	1	4
Derosa et al.2011	2	2	1	5
Hakeshzadeh et al.2010	1	1	1	3
Malaguarnera et al.2010	2	2	1	5
Mantovani et al.2010	1	0	1	2
Shakeri et al.2010	1	0	1	2
Fatouros et al.2010	2	1	1	4
Derosa et al.2010	2	2	1	5
Suchitra et al.2011	1	1	1	3
Mortazavi et al.2011	2	2	1	5
Macciò et al.2012	1	0	1	2
Karl et al.2012	2	1	1	4
Rondanelli et al.2013	1	2	1	4
Fukami et al.2013	1	0	1	2
Barzegar et al.2013	1	0	1	2
Higuchi et al.2014	1	0	1	2
Hong et al.2014	1	1	1	3
Samadi et al.2014	1	2	1	4
Soare et al.2014	1	2	1	4
Lee et al.2014	1	1	1	3
Lee et al.2015	1	1	1	3
Bañuls et al.2015	1	2	1	4
Malek Mahdavi et al.2015	2	2	1	5
Badrasawi et al.2016	2	2	1	5
Malek Mahdavi et al.2016	2	2	1	5
Jamilian et al.2017	2	2	1	5
Mohammadi et al.2017	1	2	1	4
Sharifi et al.2017	1	1	1	3
Koozehchian et al.2018	1	2	1	4
Talari et al.2019	2	2	1	5
Samulak et al.2019	0	0	1	1
Jamilian et al.2019	2	2	1	5
El-Sheikh et al.2019	1	0	1	2

Effects on oxidative status

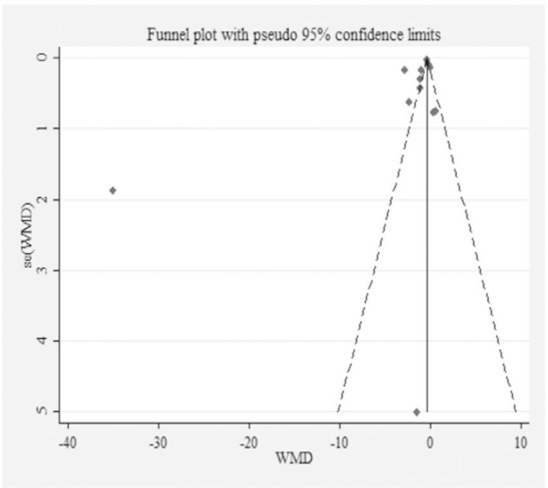
Results of our study indicated that L-carnitine supplementation was capable to the reduction of MDA and increment of SOD levels, but did not change TAC and GPX concentrations. Previously, several clinical studies have searched the effects of carnitine on oxidative stress in different diseases. In agreement with the results of present study,



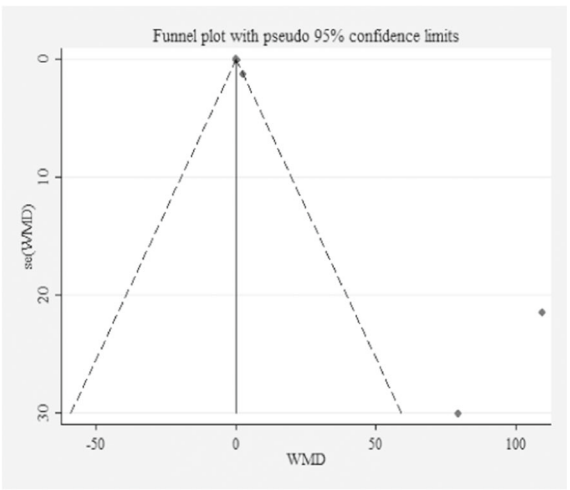
a CRP



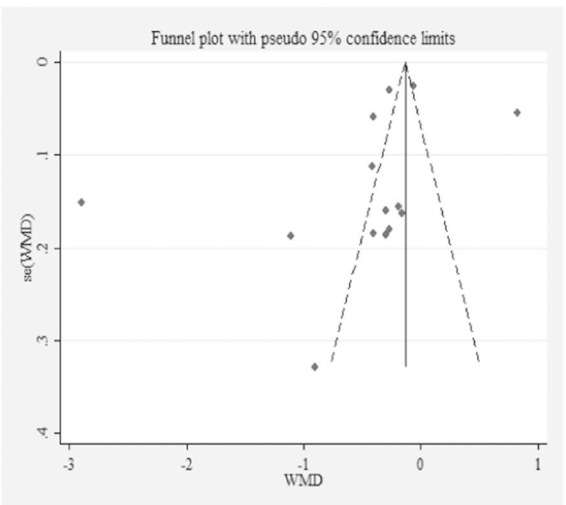
b IL-6



c TNF-a



d TAC



e MDA

Fig. 3 Funnel plots for **A**) CRP, **B**) IL-6, **C**) TNF-a, **D**) TAC and **E**) MDA

Signorelli et al. [66] reported that 600 mg propionyl L-carnitine supplementation for 12 months in hemodialysis patients with PAD was associated with improvement of oxidative parameters. In addition, taking carnitine supplements for three months by patients with age-related macular degeneration (AMD) significantly decreased MDA concentrations, while GSH levels were significantly increased [11]. Also it has been reported that carnitine administration at a dosage of 2000 mg/day for 2 months to patients with pemphigus vulgaris had favorable effects on TAC levels [49]. However, in a study by Shakeri et al. [12] 12 weeks carnitine supplementation to hemodialysis patients with hyperlipidemia did not show any significant effects on the parameters indicative of oxidative stress. Enhanced ROS generation and insufficient eliminating of free radicals lead to the alternation of function and structure of several molecules like lipids, carbohydrates, proteins, and DNA by peroxidation and glycoxidation [67, 68]. Carnitine supplementation may contribute to the modulation of oxidative stress due to its effects on the increasing of antioxidant system components like glutathione peroxidase [69], chelating of ferrous ions, interfering with the ROS formation [70], and the stabilaztion of free radicals [70, 71]. Based on all these findings as well as the results of present study, carnitine supplementation may be an effective intervention in order to the improvement of oxidative stress and protection against inflammatory status in different conditions, but these findings need to be confirmed by more RCTs in other diseases.

Strengths and limitations of study

This study is a comprehensive systematic review and meta-analysis of trials about the effect of carnitine administration on parameters of inflammation and indicators of oxidative stress. The present study had some strengths. This meta-analysis conducted on trials that investigating the efficacy of carnitine supplementation in participants with different underlying conditions. Previous meta-analyses focused on the anti-inflammatory effects of oral carnitine supplementation, but we included both oral and intravenous forms of carnitine. There are several limitations in the current meta-analysis that need to be considered in order to interpretation of the present results. In some studies, carnitine administration was combined with the supplementation of other nutrients or natural compounds to intervention group. In addition, due to the unfamiliarity with other languages, only English or Persian articles were included in this meta-analysis, which could lead to the language bias. Moreover, carnitine dosage and study duration were different in the included studies. We attempted to minimize these discrepancies trough different subgroup analyses.

Conclusions

In conclusion, carnitine supplementation lowered CRP, IL-6, TNF-α, and MDA levels, and increased SOD levels in studies conducted on healthy subjects and individuals with certain disorders, but did not affect other inflammatory parameters and oxidative stress profiles. Higher doses of L-carnitine might cause more reduction in some inflammatory variables like IL-6 and TNF-α. More RCTs in other diseases are needed to give confirmation for the findings of present work.

Author contributions HF, JH contributed in conception, design, statistical analysis and drafting of the manuscript. AM, RZ, EA, ZA and MAM contributed in data collection and manuscript drafting. All authors approved the final version for submission. JH supervised the study.

Data availability The primary data for this study is available from the authors on direct request.

Compliance with ethical standards

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no conflict of interest.

Abbreviations CRP, C-reactive protein; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α; GPx, Glutathione Peroxidase; SOD, Superoxide dismutase; TAC, Total Antioxidant Capacity; GSH, Glutathione; MDA, Malondialdehyde; ROS, Reactive Oxygen Species

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