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SYSTEMATIC REVIEWS AND META-ANALYSES

Efficacy of L-carnitine supplementation for management of blood lipids: A systematic review and dose-response meta-analysis of randomized controlled trials

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Abstract *Background and aim:* L-carnitine has an important role in fatty acid metabolism and could therefore act as an adjuvant agent in the improvement of dyslipidemia. The purpose of present systematic review and meta-analysis was to critically assess the efficacy of L-carnitine supplementation on lipid profiles.

Methods and results: We performed a systematic search of all available randomized controlled trials (RCTs) in the following databases: Scopus, PubMed, ISI Web of Science, The Cochrane Library. Mean difference (MD) of any effect was calculated using a random-effects model.

In total, there were 55 eligible RCTs included with 58 arms, and meta-analysis revealed that L-carnitine supplementation significantly reduced total cholesterol (TC) (56 arms-MD: −8.53 mg/dl, 95% CI: −13.46, −3.6, I^2: 93%), low-density lipoprotein-cholesterol (LDL-C) (47 arms-MD: −5.48 mg/dl, 95% CI: −8.49, −2.47, I^2: 94.5) and triglyceride (TG) (56 arms-MD: −9.44 mg/dl, 95% CI: −16.02, −2.87, I^2: 91.8). It also increased high density lipoprotein-cholesterol (HDL-C) (51 arms-MD:1.64 mg/dl, 95% CI:0.54, 2.75, I^2: 92.2). L-carnitine supplementation reduced TC in non-linear fashion based on dosage (r = 21.11). Meta-regression analysis indicated a linear relationship between dose of L-carnitine and absolute change in TC (p = 0.029) and LDL-C (p = 0.013). Subgroup analyses showed that L-carnitine supplementation did not change TC, LDL-C and TG in patients under hemodialysis treatment. Intravenous L-carnitine and lower doses (>2 g/day) had no effect on TC, LDL-C and triglycerides.

Conclusion: L-carnitine supplementation at doses above 2 g/d has favorable effects on patients' lipid profiles, but is modulated on participant health and route of administration.

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Introduction

Cardiovascular diseases (CVD), defined as the disorders of the heart and blood vessels; they are a leading cause of death globally of up to 17.5 million people every year [1,2]. Dyslipidemia is a major risk factor for CVD and is defined as a disturbance in circulating amounts of total cholesterol (TC), triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) [3]. Aside from drug administration, dietary modification can treat dyslipidemia [4,5]. In recent years, lipid-lowering effects of dietary supplements have been examined [6–10] which has been critically reviewed in recent studies [11–13].

L-carnitine is a quaternary ammonium cation, either synthesized in metabolically active organs including kidney, liver and brain or can be obtained from certain foods; animal products like meat, fish, poultry, and milk are the best sources [14]. Dietary intake can provide part of human body needs for carnitine [15] which reported to be between 2 and 135 mg per day [16,17]. However since carnitine could be synthesized endogenously and exogenous intake cannot affect its biosynthesis (the major source), the daily requirement of exogenous carnitine in humans is unknown [16,17] and there is no recommended daily intake for normal children and adults [16,17]. Carnitine also could be supplemented by mouth or intravenously; doses between 500 mg and 3000 mg and between 1 and 2 g oral and intravenous respectively [18].

Carnitine plays an important role in lipid metabolism through transporting long-chain fatty acids (FAs) to mitochondria where beta-oxidation occurs [19]. L-carnitine can also reduce the accumulation of harmful metabolites generated in coronary thrombosis and embolism [20–22] as well as improving adipokine concentrations [23]. Conversely insufficient carnitine is a major risk factor leading to CVD [20]. Administration of intravenous and oral carnitine at high amounts decreased mortality and heart failure among patients with CVDs [24]. Preliminary data suggest that supplementation with L-carnitine can improve insulin sensitivity in individuals with type 2 diabetes, and mild cognitive impairment and mild Alzheimer's disease [25,26]. Furthermore, patients undergoing dialysis present with low plasma carnitine levels due to removal during dialysis and impaired biosynthesis. Repeated dialysis can result in depletion of carnitine in skeletal muscle. Supplementation with carnitine has been recommended for improving health status of these patients [27].

Due to its major role in FA metabolism, L-carnitine may act as an adjuvant agent in the improvement of dyslipidemia. This could be due to the lowering effect of L-carnitine on very low-density lipoproteins (VLDL) synthesis by increasing beta-oxidation and abundance of hepatic fatty acid binding proteins [28,29]. However studies evaluating the association between L-carnitine supplementation and lipid profile have shown conflicting effects with some studies indicating an inverse relation [30–32], and other not showing any relationship [33,2,34]. We therefore conducted this systematic review and meta-analysis to summarize current findings on the effect of L-carnitine supplementation on lipid profile in adult humans.

Methods

Search strategy

Our meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [35]. The Population (aged > 18 years old), Intervention (carnitine supplementation), Comparison (matched control group), utcome (lipid profile (PICOS) model was used and included TC, LDL-C, HDL-C and TG measures that were conducted as randomized controlled trials (RCT).

The following bibliographical databases were searched, up to February 2019 with no limitation on time and language in PubMed, Scopus, Cochrane library and ISI Web of Science. Our search strategy consisted of the following medical subject headings (MeSH) and non-MeSH terms keywords: "carnitine", OR "L-carnitine" OR "levo-carnitine" OR "acetyl carnitine" OR "acetyl-L-carnitine" OR "ACAL" AND "Intervention Studies" OR "intervention" OR "controlled trial" OR "randomized" OR "randomised" OR "random" OR "randomly" OR "placebo" OR "assignment" OR randomized controlled trial OR randomized clinical trial OR RCT OR blinded OR double blind OR double blinded OR "trial" OR 'controlled clinical trial' OR Pragmatic Clinical Trial OR 'crossover procedure' OR Cross-Over trial OR Double-Blind Method OR 'equivalence trial' OR 'double blind procedure'. In addition, to ensure we collected any other relevant papers, all reference lists of eligible studies, previous review articles and trial registry platforms were searched.

Study selection and eligibility criteria

All recorded articles found from electronic or manual searches were entered into endnote software for screening (EndNote X6, Thomson Reuters, New York). The title and abstract of all articles found in the initial search were evaluated independently by two reviewers (M.A. and A.H.). All clinical trials were included in the present meta-analysis if our inclusion criteria met: (1) carried out as a RCT; (2) investigated the impact of carnitine supplementation on lipid profile including TG, TC, LDL-C and HDL-C. All studies that supplemented another compound combined with L-carnitine in both intervention and placebo group also were included; (3) presented data of interest as mean and standard deviation (SD) of lipid profiles (TC, TG, LDL-C and HDL-C) in both intervention and placebo groups; and (4) had a trial duration of more than 1 week. Articles that did not meet the eligibility criteria were excluded by using a screen form with a hierarchical approach based on study design, study population, type of intervention and outcomes measured. Exclusion criteria were (1) using a mixture of carnitine only in intervention

group, not including a placebo group; (2) semi-experimental, nonrandomized trials and trials without control groups; (3) enrolled pregnant or lactating women (4) duplicate studies with the same population (when several papers reported the same data, recent paper with largest population were included); (5) experimental and animal studies; and (6) reviews, letters to editor, editorial articles, or case reports. Any disagreements were discussed and resolved by the chief researcher (E.G.).

Data extraction

Using a pre-designed standardized electronic form (Excel, Microsoft Office), two reviewers (M.A. and A.H.) abstracted data from eligible studies: 1) the first author's last name, and year of publication; 2) trial design as crossover or parallel RCT; 3) age and number of participants; 4) trial duration, 5) dose of carnitine; 6) method of administration as oral and intravenous. Also, mean and SD of lipid profile before and after intervention were extracted. Any reported standard errors of mean (SEM), were converted to SDs through following formula by S.D = S.E.M $\times \sqrt{n}$ (n is the number of participants in each group). Finally, in studies which reported data in graphical figures, data extraction was performed by using GetData Graph Digitizer 2.24 [36].

Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [37]. The quality of all included studies were evaluated by two authors (A. S and O.S) for following items: selection bias (adequacy of sequence generation and allocation concealment), flawed outcome data (dropouts), detection (blinding), and reporting bias (selective outcome reporting) and other possible causes of bias. Based on The Cochrane Handbook recommendation, studies were ranked as low (L), or high risk of bias (H) or unclear (U) regarding each field of bias [37]. Cochrane risk of bias of included studies are outline in Supplemental Table 1.

Statistical analysis

Mean change and SD for TG, TC, HDL-C and LDL-C in the intervention and placebo groups were used to calculate effect size. As for studies with no reported SD of the mean difference, following formula were used: SD change = square root [(SD baseline 2 + SD final 2) - (2 × 0.8 × SD baseline × SD final)] [38]. Pooled effect size was estimated using the DerSimonian-Laird method. The estimates of effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). The heterogeneity across studies was evaluated by using Cochrane's Q and I^2 tests [39]. A significance level of $I^2 >$ 40% was considered as clinically important heterogeneity. To find the possible sources of between-study heterogeneity pre-planned subgroup analysis were performed based on participant's health condition (healthy/diabetic/dialysis/having hepatic disorders/other diseases), baseline body mass index (BMI), gender, study design, type of supplementation (oral or intravenous), dose and trial duration (weeks). The potential non-linear effects of L-carnitine dose (mg/day) and treatment duration (weeks) were investigated using fractional polynomial modeling [40]. Meta-regression analysis was executed to evaluate the association between pooled effect size and L-carnitine dose (mg/day). Sensitivity analysis were performed to assess the effect of each individual study on the overall estimate of effect size by removing each study in turn [41]. Publication bias was evaluated by means of Begg's rank correlation test and visual inspection of funnel plots [42]. All statistical analysis and data synthesis was performed using STATA MP V.14.0. (StataCorp, College Station, Texas, USA).

Results

Study selection

Out of 9680 provided articles in primary search, 3073 duplicated studies excluded. All title and abstracts were checked and unrelated studies excluded due to following reasons: 6520 discarded in primary evaluation of inclusion criteria: unrelated title (n = 5792), experimental studies (n = 648), letter to editor, short survey and note (n = 43), review paper and book section (n = 37). Eventually, 87 relevant studies remained; 32 other studies were excluded following full text scrutinizing: 1) performed on children and teenagers (n = 5), 2) publication which evaluate the effect of L-carnitine supplementation combined with other treatments (n = 6) 3) studies that did not report data of interest (n = 21). Finally, 55 studies with 58 arms were included for quantitative and qualitative analysis. The PRISMA flow diagram of search process is depicted in Supplemental Fig. 1.

Study characteristics

The characteristics of studies included are outlined in Table 1. In total, 3058 participants were recruited and the date of publication was between 1980 and 2018. The trial duration ranged between 2 and 54 weeks, and sample size ranged from 10 to 227 participants. All of studies were designed as parallel RCT. Selected studies enrolled subjects with different health conditions; fifteen studies enrolled patients with diabetes [34,43–56], twenty two investigated the effect of L-carnitine supplementation in patients under hemodialysis treatment [57–62,33,63,31,64–77]; two recruited patients with chronic hepatitis C diagnosis [78,79]; two enrolled dyslipidemia subjects [80,81]; single studies investigated the following health conditions: nonalcoholic steato-hepatitis [82], hypothyroidism [2], osteoarthritis [83], pemphigus vulgaris [84], rapid muscle fatigue [85], polycystic ovary syndrome [86] and coronary artery disease [87]. All other studies enrolled healthy subjects [88–90] or obese participants [32,91,92].

Some of included studies enrolled only males [32,81,87,90] or females [91,83,92,86] but most involved

Table 1 General Characteristics of included studies.

Author (location, year)	Study design	population	Sex	Number (Case/control)	Intervention Mean (range) age (years)	Intervention Mean BMI (Kg/m2)	Duration	Intervention	Route of carnitin administration	Out come
								Intervention group Comparison group		
Alavinejad et al. (Iran, 2016)	Parallel (double-blind)	Diabetic Patients	M/F	28/26	60	28.6	3 Months	L-carnitine (750 mg/day) Placebo	Oral	TC, TG
An et al. (south korea, 2016)	Parallel (double-blind)	Hypothyroidism Patients	M/F	28/25	49	24.7	12 Weeks	L-carnitine (1980 mg/day) Placebo	Oral	TC, TG, HDL, LDL (Not reported)
Bloomer et al. (USA, 2009)	Parallel (double-blind)	Pre Diabetic Patients	M/F	14/15	31	28.5	8 Weeks	Acetyl L-carnitine Arginate (3 g/day) Placebo	Oral	TC, HDL, LDL (Equation)
Brescia et al. (Italy, 2002)	Parallel (open-label trial)	Diabetic Patients with Hyperlipidemia	M/F	16/16	>30	NR	2 Months	L-carnitine (2 g/day) plus Simvastatin (20 mg/day) Simvastatin (20 mg/day)	Oral	TC, TG, HDL
Delas et al. (Croatia, 2008)	Parallel (double-blind)	Healthy Sedentary Population	M/F	18/12	23.1	22.7	2 Weeks	L-carnitine (2 g/day) Placebo	Oral	TC, TG, HDL
Derosa et al. (Italy, 2003)	Parallel (double-blind)	Hypercholesterolemic Patients with Type 2 Diabetes	M/F	46/48	52	27.3	6 Months	L-carnitine (2 g/day) plus controlled-energy diet Placebo plus controlled-energy diet	Oral	TC, TG, HDL, LDL (Equation)
Derosa et al. (Italy, 2011)	Parallel (double-blind)	Diabetic patients	M/F	113/110	54	33.9	12 Months	L-carnitine (2 g/day) plus Sibutramine (10 mg/day) Sibutramine (10 mg/day)	Oral	TC,TG, HDL, LDL (Equation)
Derosa et al. (Italy, 2011)	Parallel (double-blind)	Diabetic patients	M/F	114/113	51	32.9	12 Months	L-carnitine (2 g/day) plus Orlistat (360 mg/day) Orlistat (360 mg/day)	Oral	TC, TG, HDL, LDL (Equation)
Duranay et al. (Turkey, 2006)	Parallel (open-label trial)	Hemodialysis Patients	M/F	21/21	44	23.4	6 Months	L-carnitine (20 mg/kg/three times per week) No Placebo	Intravenous	TC, TG, LDL (Equation)
Elsheikh et al. (Egypt, 2018)	Parallel (open-label trial)	Type 2 Diabetes Mellitus Patients	M/F	31/27	50.9	34.4	6 Months	L-carnitine (2 g/day) plus Glimepiride (4 mg/day) Glimepiride (4 mg/day)	Oral	TC, TG, HDL, LDL (Equation)
EmamiNaini et al. (Iran, 2012)	Parallel (double-blind)	Hemodialysis Patients	M/F	24/27	53.9	23	16 Weeks	L-carnitine (1 g/day) Placebo	Oral	TC, TG, HDL, LDL (Equation)
Eshghinia et al. (Iran, 2014)	Parallel (double-blind)	Hemodialysis Patients	M/F	17/17	45.1	23.1	16 Weeks	L-carnitine (2 g/day) Placebo	Oral	TC, TG, HDL, LDL (Not reported)
Florentin et al. (Greece, 2016)	Parallel (double-blind)	Dyslipidemia Patients	M/F	29/29	53	29	12 Weeks	L-Carnitine (2 g/day) plus Simvastatin (20 mg/day) Placebo plus Simvastatin (20 mg/day)	Oral	TC, TG, HDL, LDL (Equation)
Fukami et al. (Japan, 2013)	Parallel (open-label trial)	Hemodialysis Patients	M/F	32/38	68	22.3	6 Months	L-carnitine (900 mg/day) Placebo	Oral	TG, HDL, LDL (Not reported)
Galvano et al. (Italy, 2009)	Parallel (double-blind)	Type 2 Diabetes Mellitus Patients	M/F	38/37	52.1	28.2	4 Months	L-carnitine (2 g/day) plus Simvastatin (20 mg/day) Simvastatin (20 mg/day)	Oral	TC, TG, HDL, LDL (Equation)
Golper et al. (USA, 1990)	Parallel (double-blind)	Hemodialysis Patients	M/F	26/33	47.5	NR	6 Months	L-carnitine (20 mg/kg/three times per week) Placebo	Intravenous	TC, HDL, LDL (Equation)

Gonzalez-Ortiz et al. (Mexico, 2008)	Parallel (double-blind)	Type 2 Diabetes Mellitus Patients	M/F	6/6	44.1	27.5	4 Weeks	L-carnitine (3 g/day) Placebo	Oral	TC, TG, HDL, LDL (Equation)
Guarnieri et al. (Italy, 1980)	Parallel (single-blind)	Hemodialysis Patients	M/F	8/8	24–66	NR	14 Weeks	L-carnitine (0.5–1 g/three times per week) Placebo	Intravenous	TG, TC
Hakimi et al. (Iran, 2015)	Parallel (double-blind)	Obese Male	M	12/12	23.6	32.2	8 Weeks	L-carnitine (3 g/day) plus Resistance and Endurance training program (3 times a week for 8 weeks) Placebo plus Resistance and Endurance training program (3 times a week for 8 weeks)	Oral	TC, TG, HDL, LDL (Equation)
Higuchi et al. (Japan, 2014)	Parallel (open-label trial)	Hemodialysis Patients	M/F	67/64	67	NR	12 Months	L-carnitine (20 mg/kg/day) No Placebo	Oral	TC, TG, LDL (Not reported)
Higuchi et al. (Japan, 2016)	Parallel (open-label trial)	Hemodialysis Patients	M/F	72/73	66	22	12 Months	L-carnitine (20 mg/kg/day) No Placebo	Oral	TC, TG, LDL (Not reported)
Hlais et al. (Lebanon, 2012)	Parallel (single-blind)	Dyslipidemic Patients	M	15/19	55.6	31.3	12 Weeks	L-carnitine (1 g/day) Placebo	Oral	TC,TG, HDL, LDL (Direct)
Karimi et al. (Iran, 2012)	Parallel (double-blind)	Obese Women	F	11/11	34.8	33.3	8 Weeks	L-carnitine (2 g/day) plus aerobic training Placebo plus aerobic training	Oral	TC, TG, HDL, LDL (Equation)
Karimi et al. (Iran, 2012)	Parallel (double-blind)	Obese Women	F	11/11	34.4	33.9	8 Weeks	L-carnitine (2 g/day) Placebo	Oral	TC, TG, HDL, LDL (Equation)
Kudoh et al. (Japan, 2014)	Parallel (double-blind)	Chronic Hemodialysis Patients	M/F	9/6	66.2	NR	3 Months	L-carnitine (900 mg/day) Placebo	Oral	TC, TG, HDL, LDL (Not reported)
Labonia et al. (Argentina, 1995)	Parallel (double-blind)	Hemodialysis Patients	M/F	13/11	41.8	NR	6 Months	L-carnitine (1 g/day) Placebo	Intravenous	TC, TG, HDL
Lee et al. (Taiwan, 2016)	Parallel (single-blind)	Coronary Artery Disease	M	20/19	71.9	NR	12 Weeks	L-carnitine (1 g/day) Placebo	Oral	TC, TG, HDL, LDL (Direct)
Liang et al. (China,1998)	Parallel (double-blind)	Diabetic Patients	M/F	23/23	59.4	27.2	12 Weeks	L-carnitine (3 g/day) Placebo	Oral	TC, TG, HDL
Mahdavi et al. (Iran, 2015)	Parallel (double-blind)	Obese women with knee osteoarthritis	F	33/36	51.6	31.5	8 Weeks	L-carnitine (750 mg/day) Placebo	Oral	TC, TG, HDL, LDL (Equation)
Malaguarnera et al. (Italy, 2002)	Parallel (open-label trial)	Chronic Hepatitis C	M/F	14/11	56.8	26	6 Months	L-carnitine (2 g/day) plus IFNα (3 million IU three times a week) IFNα (3 million IU three times a week)	Oral	TC, TG, HDL, LDL (Equation)
Malaguarnera et al. (Italy, 2007)	Parallel (double-blind)	Centenarians	M/F	27/27	101	22.2	6 Months	L-carnitine (2 g/day) Placebo	Oral	TC, TG, HDL
Malaguarnera et al. (Italy, 2008)	Parallel (double-blind)	Diabetic Patients	M/F	41/40	49	27.4	3 Months	L-carnitine (2 g/day) Placebo	Oral	TC, TG, HDL, LDL (Equation)

(*continued on next page*)

Table 1 (*continued*)

Author (location, year)	Study design	population	Sex	Number (Case/control)	Intervention Mean (range) age (years)	Intervention Mean BMI (Kg/m2)	Duration	Intervention Intervention group Comparison group	Route of carnitin administration	Out come
Malaguarnera et al. (Italy, 2010)	Parallel (double-blind)	Nonalcoholic Steatohepatitis	M/F	36/38	47.9	26.6	24 Weeks	L-carnitine (2 g/day) plus ad libitum diet placebo plus ad libitum diet	Oral	TC, TG, HDL, LDL (Equation)
Mitwalli et al. (KSA, 2005)	Parallel (single-blind)	Hemodialysis Patients	M/F	18/13	54	NR	6 Months	L-carnitine (15 mg/kg/three times per week) Placebo	intravenous	TC, TG
Mohammadi et al. (Iran, 2017)	Parallel (double-blind)	Patients with Pemphigus Vulgaris	M/F	26/26	41	28	8 Weeks	L-carnitine (2 g/day) Placebo	Oral	TC, TG, HDL, LDL (Direct)
Mortazavi et al. (Iran, 2012)	Parallel (double-blind)	Hemodialysis Patients	M/F	17/19	54	NR	6 Months	L-carnitine (750 mg/day) Placebo	Oral	TC, TG, HDL, LDL (Not reported)
Mosah et al. (Iraq, 2015)	Parallel (single-blind)	Obese Females	F	18/18	33.1	34.5	12 Weeks	L-carnitine (1 g/day) No Placebo	Oral	TC, TG, HDL, LDL (Not reported)
Nilsson-ehle et al. (Sweden, 1985)	Parallel (double-blind)	Hemodialysis Patients	M/F	14/14	24–65	NR	6 Weeks	L-carnitine (2 g/three times per week) Placebo	Intravenous	TC, TG, HDL, LDL (Equation)
Odo et al. (Japan, 2013)	Parallel (double-blind)	Healthy Volunteers	M	5/5	44.4	26.6	4 Weeks	L-carnitine (500 mg/day) plus motivation training placebo plus motivation training	Oral	TC, TG, HDL, LDL (Not reported)
Odo et al. (Japan, 2013)	Parallel (double-blind)	Healthy Volunteers	M	6/5	43.3	25.8	4 Weeks	L-carnitine (500 mg/day) placebo	Oral	TC, TG, HDL, LDL (Not reported)
Parvanova et al. (UK, 2018)	Parallel (double-blind)	Type 2 Diabetes Mellitus Patients	M/F	109/110	64.9	30	6 Months	Acetyl L-carnitine (2 g/day) plus Simvastatin (10–20 mg/day) Placebo plus Simvastatin (10–20 mg/day)	Oral	TC, TG, HDL, LDL (Not reported)
Pistone et al. (Italy, 2003)	Parallel (double-blind)	Elderly Subjects with Rapid Muscle Fatigue	M/F	42/42	81.5	25.7	1 Month	L-carnitine (4 g/day) plus ad libitum diet placebo plus ad libitum diet	Oral	TC, TG, HDL, LDL (Not reported)
Rahbar et al. (Iran, 2005)	Parallel (double-blind)	Type 2 Diabetes Mellitus Patients	M/F	19/16	50.5	27.9	12 Weeks	L-carnitine (3 g/day) placebo	Oral	TC, TG, HDL, LDL (Equation)
Rathod et al. (India, 2006)	Parallel (single-blind)	Hemodialysis Patients	M/F	10/10	40.3	NR	8 Weeks	L-carnitine (20 mg/kg/three times per week) Placebo	Intravenous	TC, TG, HDL, LDL (Not reported)
Romano et al. (Italy, 2007)	Parallel (double-blind)	Chronic Hepatitis C	M/F	35/35	50.1	25.8	12 Months	L-carnitine (2 g/day) plus IFNα (3 million IU three times a week) plus ribavirin (1000 mg per day) IFNα (3 million IU three times a week) plus ribavirin (1000 mg per day)	Oral	TC, TG, HDL, LDL (Equation)
Sakurabayashi et al. (Japan, 2008)	Parallel (open-label trial)	Hemodialysis Patients	M/F	10/10	45.7	NR	12 Months	L-carnitine (500 mg/three times per week) No Placebo	Oral	TC, TG, HDL
Samimi et al. (Iran, 2015)	Parallel (double-blind)	Polycystic Ovary Syndrome	F	30/30	25.5	28.9	12 Weeks	L-carnitine (250 mg/day) placebo	Oral	TC, TG, HDL, LDL (Direct)

Santo et al. (Italy, 2006)	Parallel (double-blind)	Type 2 Diabetic Patients with Peripheral Arterial Disease	M/F	37/37	61.7	34	12 Months	Propionyl L-carnitine (2 g/day) plus Standard diet with 0/9 g/kg/day Placebo plus Standard diet with 0/9 g/kg/day	Oral	TC, TG, HDL, LDL (Direct)
Shojaei et al. (Iran, 2011)	Parallel (double-blind)	Hemodialysis Patients	M/F	14/13	52.8	23.3	3 Months	L-carnitine (1 g/three times per week) plus coenzyme Q10 (100 mg/day) coenzyme Q10 (100 mg/day)	Intravenous	TC, TG, HDL, LDL (Direct)
Shojaei et al. (Iran, 2011)	Parallel (double-blind)	Hemodialysis Patients	M/F	12/13	55.3	24.3	3 Months	L-carnitine (1 g/three times per week) Placebo	Intravenous	TC, TG, HDL, LDL (Direct)
Sohn et al. (South Korea, 1992)	Parallel (double-blind)	Hemodialysis Patients	M/F	15/15	46.2	NR	2 Months	L-carnitine (1−1.5 g/three times per week) Placebo	Intravenous	TC, TG, HDL, LDL (Not reported)
Solfrizzi et al. (Italy, 2005)	Parallel (open-label trial)	Type 2 Diabetes Mellitus Patients	M/F	26/26	65.4	29	2 Months	L-carnitine (2 g/day) plus Simvastatin (20 mg/day) Simvastatin (20 mg/day)	Oral	TC, TG, HDL, LDL (Equation)
Steiber et al. (USA, 2006)	Parallel (double-blind)	Hemodialysis Patients	M/F	15/19	67.6	30.4	24 Weeks	L-carnitine (20 mg/kg/three times per week) Placebo	Intravenous	TG, HDL
Suchitra et al. (India, 2011)	Parallel (single-blind)	Hemodialysis Patients	M/F	20/15	50.2	21.8	6 Months	L-carnitine (1 g/three times per week) No Placebo	Intravenous	TC, TG, HDL, LDL (Equation)
Vaux et al. (UK, 2004)	Parallel (double-blind)	Hemodialysis Patients	M/F	13/13	58.8	NR	16 Weeks	L-carnitine (20 mg/kg/three times per week) Placebo	Intravenous	TC, TG
Vesela et al. (Czech Republic, 2001)	Parallel (open-label trial)	Hemodialysis Patients	M/F	12/12	55.5	NR	9 Months	L-carnitine (15 mg/kg/three times per week) No Placebo	Intravenous	TC, TG, HDL, LDL (Equation)
Weschler et al. (Israel, 1984)	Parallel (double-blind)	Hemodialysis Patients	M/F	6/4	50.8	NR	5 Weeks	L-carnitine (3 g/day) placebo	Oral	TC, TG, HDL, LDL (Not reported)
Yderstraede et al. (Denmark, 1987)	Parallel (double-blind)	Hemodialysis Patients	M/F	10/10	49	NR	6 Weeks	L-carnitine (100 μmol/L) No Placebo	Intravenous	TC, TG, HDL, LDL (Equation)

both genders [34,2,43,44,88,45–47,57,48,58,80,59,49,60,50,61,62,33,63,51,89,82,78,52,31,84,64,53,85,54,79,65,55,66,56,67–77]. In addition studies performed in subjects with different baseline BMI; ten in subjects under 24.9 kg/m^2 [2,88,57–59,62,89,66–68], 17 with a BMI between 25 kg/m and 29.9 kg/m^2 [34,43,45,80,49–51,82,78,52,84,90,85,54,79,86,56] and 10 with a BMI over than 30 kg/m^2 [46–48,32,81,91,83,92,53,55]; whilst 18 did not report BMI [44,60,61,33,63,87,31,64,65,69–77]. Among included studies fourteen studies administered L-carnitine intravenously [57,60,63,31,66,67,69–75,77], but in forty-one RCTs an oral route of administration was investigated [34,2,43,44,88,45–48,58,80,59,49,50,32,61,62,81,91,33,87,51,83,89,82,78,52,84,64,92,90,53,85,54,79,65,86,55,56,68,76]. Although 2 studies used Acetyl L-carnitine [43,53], and one study propionyl L-carnitine [55] the majority of RCTs (52 studies) used L-carnitine [34,2,44,88,45–47,57,48,58,80,59,49,60,50,32,61,62,81,91,33,63,87,51,83,89,82,78,52,31,84,64,92,90,85,54,79,65,86,66,56,67–77]. All of included studies were in English except two studies which were in Persian [32,91] and one in Korean [72].

Outcome measure also depicted in Table 1. Regarding different methods for assessing LDL-C, it must be noted that most of included studies used Friedewald method for calculating LDL-C except six studies which used direct method [81,87,84,86,55,66]. Although thirteen studies did not report the exact method of measurement [68,27,62,64,92,90,53,85,79,72,76].

Results from quality assessments

Random allocation of participants was mentioned in all included trials. Nevertheless, twenty-two trials described the method of random sequence generation [34,2,45–47,58,83,89,82,78,52,84,64,53,85,54,71,79,86,55,66,73]. Twenty-four trials reported allocation concealment [2,43,88,45–47,58,61,62,91,33,63,51,83,89,82,52,84,64,90,53,85,54,86,56]. Fourteen trials had high risk of bias regarding blinding of participants and personnel [44,57,48,59,61,62,87,78,31,92,65,56,67] and two studies had high risk of bias regarding blinding outcome assessors [57,30]. Most studies showed low risk of bias based on incomplete outcome data; nevertheless, 6 studies had unclear risk of bias [45,57,49,32,92,67]. Twenty-two studies had low risk of bias regarding selective reporting [34,2,48,58,68,59,69,61,62,87,84,64,53,71,86,70,72,56,73,74,76,77]. All of studies had unclear risk of bias regarding other potential threats to validity. Details of risk of bias assessment are described in Supplementary Table 1.

Meta-analysis results

Effect of L-carnitine supplementation on total cholesterol

The overall result of our meta-analysis of 56 arms (1506 cases and 1482 control subjects) showed that there was a significant reduction in TC (WMD −8.53 mg/dL; 95% CI: −13.46, −3.6, $p = 0.001$), with considerable heterogeneity between studies ($p < 0.001$, $I^2 = 93\%$) (Fig. 1).

To find any source of heterogeneity, we performed subgroup analyses based on gender (male/female/gender), baseline BMI (normal/overweight/obese), participants' health condition (healthy/diabetic/dialysis/having hepatic disorders/other diseases), dose of L-carnitine (<2/≥2 g/d), study duration (≤6/>6 months) and type of intervention (oral and intravenous). Subgroup analysis based on baseline BMI could explain between-study heterogeneity. This also indicated a significant lowering effect of L-carnitine supplementation on TC in all subgroups except in RCTs used <2 g/d L-carnitine, intravenous administration or studies on hemodialysis patients (Table 2).

Effect of L-carnitine supplementation on LDL-cholesterol

The effect of the L-carnitine supplementation on LDL-C was evaluated in forty-seven arms of clinical trials (1364 cases and 1361 control subjects) and pooled mean difference from inverse variance method showed a reduction in LDL-C of −5.48 mg/dL (95% CI: −8.49, −2.47, $p = <0.001$) with considerable between-study heterogeneity ($p < 0.001$, $I^2 = 94.5$) (Fig. 1).

All of above-mentioned subgroup analysis indicated that gender explained potential between-study heterogeneity. L-carnitine supplementation decreased LDL-C in all subgroups except in RCTs which administered <2 g/d, those that administered L-carnitine intravenously, RCTs performed on hemodialysis patients and those that included patients with BMI of <25 kg/m^2 (Table 2).

Effect of L-carnitine supplementation on HDL-cholesterol

Overall, 51 arms of included clinical trials (1326 cases and 1321 control subjects) investigated the effect of L-carnitine supplementation on HDL-C concentration, and pooled effect size showed a significant increased serum HDL-C concentration (WMD = 1.64 mg/dL; 95% CI: 0.543, 2.75, p = 0.003), with between-study heterogeneity (P < 0.001, $I^2 = 92.2$) (Fig. 1).

Subgroup analysis revealed that L-carnitine supplementation resulted in a significant increase in HDL-C concentrations in all subgroups except in RCTs with an intervention duration of >6 months (Table 2).

Effect of L-carnitine supplementation on triglyceride

Fifty-six arms of RCTs (1513 cases and 1491 control subjects) reported the effect of L-carnitine supplementation on TG concentrations, and combining effect sizes from these studies revealed a significant reduction in TG (WMD = −9.44 mg/dL; 95% CI: −16.23, −2.87, $p = 0.005$), with a significant between-study heterogeneity ($p < 0.001$, $I^2 = 91.8$) (Fig. 1). To find the probable source of heterogeneity, subgroup analysis was conducted. Dividing RCTs based on gender subgroups could explain between study heterogeneity. Which was accounted for in those RCTs that administered <2 g/d L-carnitine, or for longer than 6

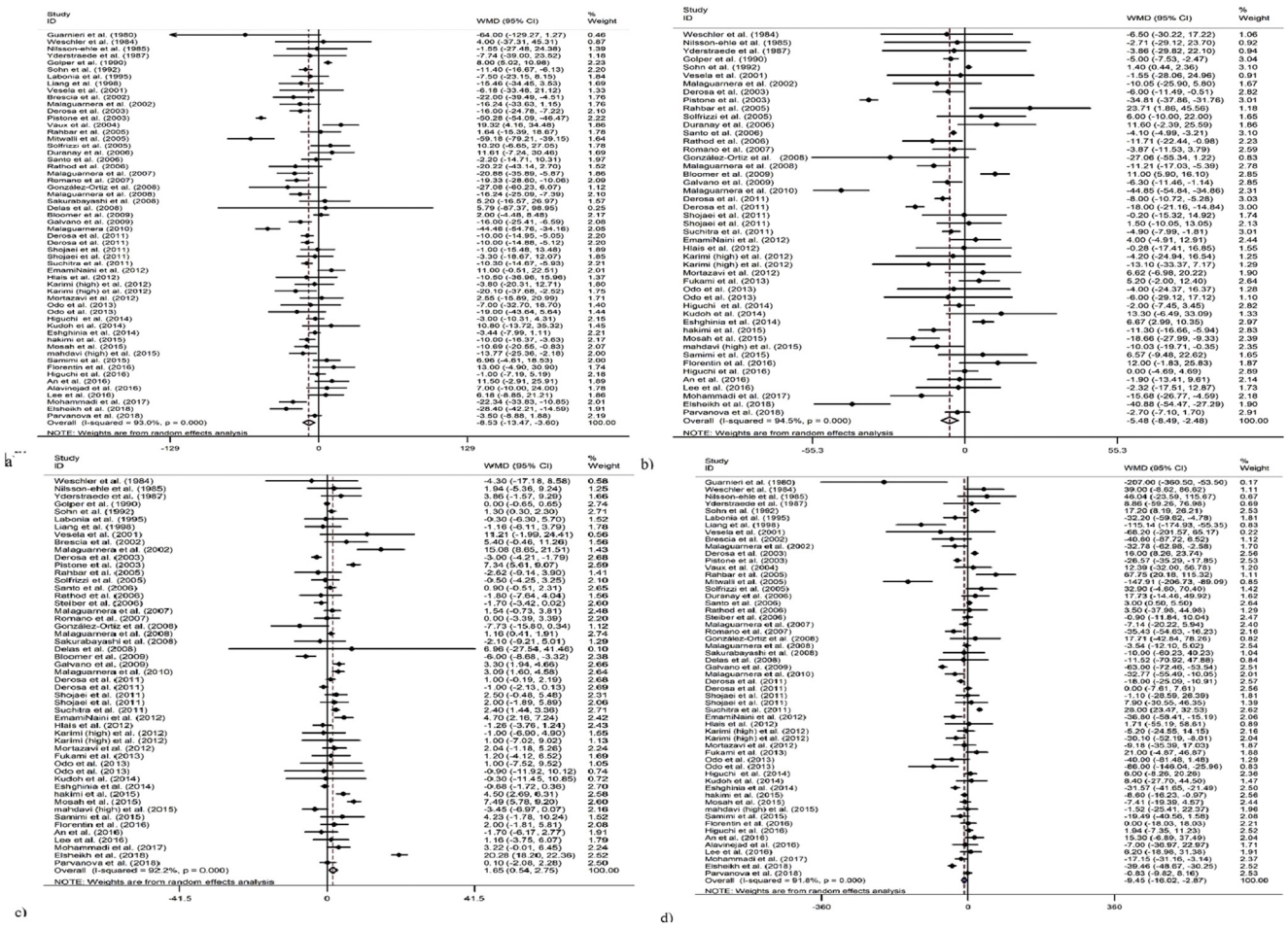

Figure 1 Forest plot presenting mean difference (MD) and 95% confidence intervals for the impact of L-carnitine supplementation on a) TC (mg/dl), b) LDL-C (mg/dl), c) HDL-C (mg/dl) and d) TG (mg/dl).

months, as well as studies that included individuals with baseline BMI of <25 kg/m^2, those that used intravenous L-carnitine and studies with patients under hemodialysis and those with diabetes and dyslipidemia (Table 2).

Furthermore, subgroup analysis was performed based on combination of L-carnitine with other factors (exercise, drugs etc.) as part of the protocol or when prescribed alone. Although intervention group receive the same intervention compared with control group plus L-carnitine supplementation, but this subgroup was performed to find possible synergistic effect of L-carnitine with other lifestyle modifications. As shown in Table 2, all lipid profiles except TG remained significant in both subgroups.

Sensitivity analysis

Sensitivity analysis for TC showed that the overall estimates were influenced by elimination of studies conducted by Mitwalli et al. [31] (−7.68 mg/dl, 95%CI: −12.6, −2.77), Pistone et al. [85] (−7.48 mg/dl, 95%CI: −10.89, −4.07), Vaux et al. [74] (−9.06 mg/dl, 95%CI: −14.01, −4.1) and Malaguarnera (2010) [82] (−7.77 mg/dl, 95%CI: −12.66, −2.89); although remained statistically significant. Exclusion of studies carried-out by Malaguarnera et al. (2010) [82] (−4.57 mg/dl, 95% CI: −7.53, −1.62), Pistone et al. [85] (−4.63 mg/dl, 95%CI: −7.01, −2.26), and Elsheikh et al. [48] (−4.81 mg/dl, 95% CI: −7.81, −1.81) changed the overall effect size for LDL-C. In addition, the results of sensitivity analysis for HDL-C showed that removing the Elsheikh et al., [48] study, changed the overall effect size (1.18 mg/dl 95%CI: 0.35, 2.02). Finally exclusion of Galvano et al. [49] and Suchitra et al. [67] studies changed the overall effect size for TG as well (−7.82 mg/dl (−13.81, −1.83) and −10.37 mg/dl (−16.54, −4.2) respectively).

Publication bias

There was no evidence of publication bias for studies examining the effect of L-carnitine supplementation on HDL-C (p = 0.839, Begg's test), LDL-C (p = 0.404, Begg's test), TC (p = 0.553, Begg's test) and TG (p = 0.767, Begg's test).

Non-linear dose-responses between dose and duration of L-carnitine supplementation and lipid profile components

Dose-response analysis showed that L-carnitine supplementation changed TC significantly based on dose (r = 21.11, P-nonlinearity = 0.036) in non-linear fashion. At

Table 2 Subgroup analysis to assess the effect of carnitine supplementation on lipid profile.

Subgrouped by	No. of trials	WMD (95% CI)			P Value	P for heterogeneity	I^2 (%)	P for between subgroup heterogeneity
Total Cholesterol								
Total	56	−8.533	−13.465	−3.601	0.001	<0.001	93	
Gender								0.654
Male	5	−8.198	−13.648	−2.748	0.003	0.331	13	
Female	5	−7.454	−13.036	−1.872	0.009	0.046	58.7	
Both	46	−9.717	−10.950	−8.485	<0.001	<0.001	93	
Baseline BMI								<0.001
<25 kg/m2	10	−4.321	−6.856	−1.786	0.001	0.001	84.1	
25−30 kg/m2	18	−25.500	−27.796	−23.203	<0.001	<0.001	95.2	
>30 kg/m2	11	−9.266	−11.626	−6.906	<0.001	0.106	36.6	
Dosage								<0.001
<2 g	28	−1.146	−2.774	0.483	0.168	<0.001	80.7	
≥2 g	27	−18.710	−20.410	−17.009	<0.001	<0.001	94	
Intervention Duration (Weeks)								0.114
≤6 months	48	−10.028	−11.347	−8.709	<0.001	<0.001	93.9	
> 6 months	8	−7.687	−10.277	−5.096	<0.001	0.026	56	
Type of Study Population								<0.001
Healthy	9	−34.072	−36.976	−31.168	<0.001	<0.001	95.3	
Hemodialysis	22	−0.976	−2.697	0.745	0.266	<0.001	82.9	
Diabetes and Dyslipidemia	17	−8.067	−10.241	−5.893	<0.001	<0.001	68	
Hepatic Disorders	3	−28.632	−35.039	−22.225	<0.001	0.001	86.6	
Miscellaneous	5	−4.311	−9.925	1.303	0.132	<0.001	81.9	
Type of Intervention								<0.001
Oral	42	−13.572	−14.995	−12.150	<0.001	<0.001	92.9	
Intravenous	14	−0.884	−2.971	1.202	0.406	<0.001	88.8	
Type of Supplementation								0.920
Alone	40	−9.507	−10.906	−8.109	<0.001	<0.001	94.8	
Combined with Other Lifestyle Modification	16	−9.639	−11.808	−7.470	<0.001	0.001	59.8	
Low Density Lipoprotein								
Total	**47**	**−5.485**	**−8.493**	**−2.477**	**<0.001**	**<0.001**	**94.5**	
Gender								0.003
Male	5	−9.078	−13.701	−4.455	<0.001	0.602	0	
Female	5	−10.958	−16.657	−5.259	<0.001	0.104	47.9	
Both	37	−3.567	−4.106	−3.027	<0.001	<0.001	95.5	
Baseline BMI								<0.001
<25 kg/m2	9	0.654	−1.233	2.542	0.497	0.001	70.8	
25−30 kg/m2	16	−15.237	−17.045	−13.429	<0.001	<0.001	95.9	
>30 kg/m2	11	−5.673	−6.460	−4.885	<0.001	<0.001	91.2	
Dosage								<0.001
<2 g	23	0.311	−0.474	1.096	0.437	<0.001	72.1	
≥2 g	23	−7.154	−7.882	−6.427	<0.001	<0.001	96.1	
Intervention Duration (Weeks)								<0.001
≤6 months	40	−2.518	−3.239	−1.797	<0.001	<0.001	94.6	
>6 months	7	−5.142	−5.935	−4.349	<0.001	<0.001	92.4	
Type of Study Population								<0.001
Healthy	7	−27.102	−29.580	−24.623	<0.001	<0.001	92.1	
Hemodialysis	18	0.522	−0.273	1.317	0.198	<0.001	70.5	
Diabetes and Dyslipidemia	14	−5.073	−5.839	−4.306	<0.001	<0.001	91.9	
Hepatic Disorders	3	−17.903	−23.579	−12.227	<0.001	<0.001	95.2	
Miscellaneous	5	−6.755	−12.134	−1.376	0.014	0.159	39.3	
Type of Intervention								<0.001
Oral	37	−6.212	−6.898	−5.526	<0.001	<0.001	94.6	
Intravenous	10	0.138	−0.711	0.987	0.75	<0.001	77.7	
Type of Supplementation								<0.001
Alone	32	−2.061	−2.802	−1.320	<0.001	<0.001	95.4	
Combined with Other Lifestyle Modification	15	−5.472	−6.241	−4.703	<0.001	<0.001	87.7	
High Density Lipoprotein								
Total	**51**	**1.648**	**0.543**	**2.752**	**0.003**	**<0.001**	**92.2**	
Gender								<0.001
Male	5	2.320	0.944	3.695	0.001	0.007	71.6	
Female	5	4.820	3.398	6.243	<0.001	<0.001	88.6	
Both	41	1.118	0.845	1.391	<0.001	<0.001	92.9	

Table 2 (*continued*)

Subgrouped by	No. of trials	WMD (95% CI)			P Value	P for heterogeneity	I^2 (%)	P for between subgroup heterogeneity
Baseline BMI								<0.001
<25 kg/m2	9	1.279	0.662	1.896	<0.001	<0.001	72	
25–30 kg/m2	17	1.247	0.772	1.723	<0.001	<0.001	90.4	
>30 kg/m2	12	2.141	1.622	2.661	<0.001	<0.001	97.3	
Dosage								0.010
<2 g	23	0.884	0.506	1.262	<0.001	<0.001	81.3	
≥2 g	27	1.661	1.293	2.029	<0.001	<0.001	94.9	
Intervention Duration (Weeks)								0.001
≤6 months	45	1.476	1.192	1.761	<0.001	<0.001	92.9	
> 6 months	6	0.190	−0.499	0.880	0.588	0.073	50.4	
Type of Study Population								<0.001
Healthy	9	5.377	4.479	6.275	<0.001	<0.001	73.8	
Hemodialysis	18	0.657	0.260	1.054	0.001	<0.001	66	
Diabetes and Dyslipidemia	16	0.984	0.575	1.392	<0.001	<0.001	96.5	
Hepatic Disorders	3	3.127	1.796	4.459	<0.001	<0.001	87.9	
Miscellaneous	5	0.371	−1.467	2.209	0.692	0.040	60.1	
Type of Intervention								0.004
Oral	40	1.573	1.246	1.900	<0.001	<0.001	93.5	
Intravenous	11	0.767	0.324	1.211	0.001	<0.001	68.5	
Type of Supplementation								0.111
Alone	35	1.148	0.832	1.463	<0.001	<0.001	84	
Combined with Other Lifestyle Modification	16	1.613	1.135	2.090	<0.001	<0.001	96.5	
Triglyceride								
Total	**56**	**−9.447**	**−16.023**	**−2.872**	**0.005**	**<0.001**	**91.8**	
Gender								0.005
Male	5	−16.415	−38.216	5.386	0.140	0.040	60.0	
Female	5	−11.496	−20.532	−2.460	0.013	0.310	16.5	
Both	46	−8.329	−15.852	−0.805	0.030	<0.001	93	
Baseline BMI								<0.001
<25 kg/m2	11	0.333	−17.001	17.667	0.970	<0.001	93.5	
25–30 kg/m2	17	−18.759	−34.347	−3.170	0.018	<0.001	92.8	
>30 kg/m2	12	−9.350	−17.653	−1.048	0.027	<0.001	89.9	
Dosage								<0.001
<2 g	29	−7.306	−17.572	2.961	0.163	<0.001	88.1	
≥2 g	26	−12.475	−21.315	−3.636	0.006	<0.001	93.2	
Intervention Duration (Weeks)								<0.001
≤6 months	48	−10.104	−18.863	−1.345	0.024	<0.001	92.4	
> 6 months	8	−5.869	−14.928	3.190	0.204	<0.001	84.5	
Type of Study Population								<0.001
Healthy	9	−16.273	−25.463	−7.083	0.001	0.005	63.5	
Hemodialysis	23	−3.127	−15.403	9.150	0.618	<0.001	89.3	
Diabetes and Dyslipidemia	16	−9.186	−21.378	3.007	0.140	<0.001	95.1	
Hepatic Disorders	3	−34.028	−47.219	−20.837	<0.001	0.981	52.9	
Miscellaneous	5	−4.903	−18.413	8.606	0.477	0.075	0	
Type of Intervention								<0.001
Oral	42	−11.412	−18.111	−4.713	0.001	<0.001	90.3	
Intravenous	14	−1.712	−17.079	13.654	0.827	<0.001	84.8	
Type of Supplementation								0.000
Alone	40	−7.433	−16.366	1.500	<0.001	0.103	88.8	
Combined with Other Lifestyle Modification	16	−13.836	−24.941	−2.731	<0.001	0.015	95	

higher doses a decreased trend for TC was found. Furthermore, the dose of L-carnitine affected LDL-C (r = 18.87, P-nonlinearity = 0.057) and HDL-C based on study duration (r = −0.252, P-nonlinearity = 0.052) in a non-linear fashion. Significant associations were not observed for other outcomes in non-linear dose-responses (Fig. 2).

Meta-regression analysis

Meta-regression using the random-effects model was undertaken to investigate the potential association between a decrease in lipid profile risk and dose of L-carnitine (mg/day). Meta-regression analysis indicated a linear relationship between dose absolute changes in TC ($p = 0.029$) and LDL-C ($p = 0.013$) (Fig. 3), but not for TG ($p = 0.868$) or HDL-C ($p = 0.910$) (Table 3).

Discussion

We found that L-carnitine supplementation resulted in a clear improvement in lipid profile with reduced TC, LDL-C and TG, whereas HDL-C was raised. In terms of dose-

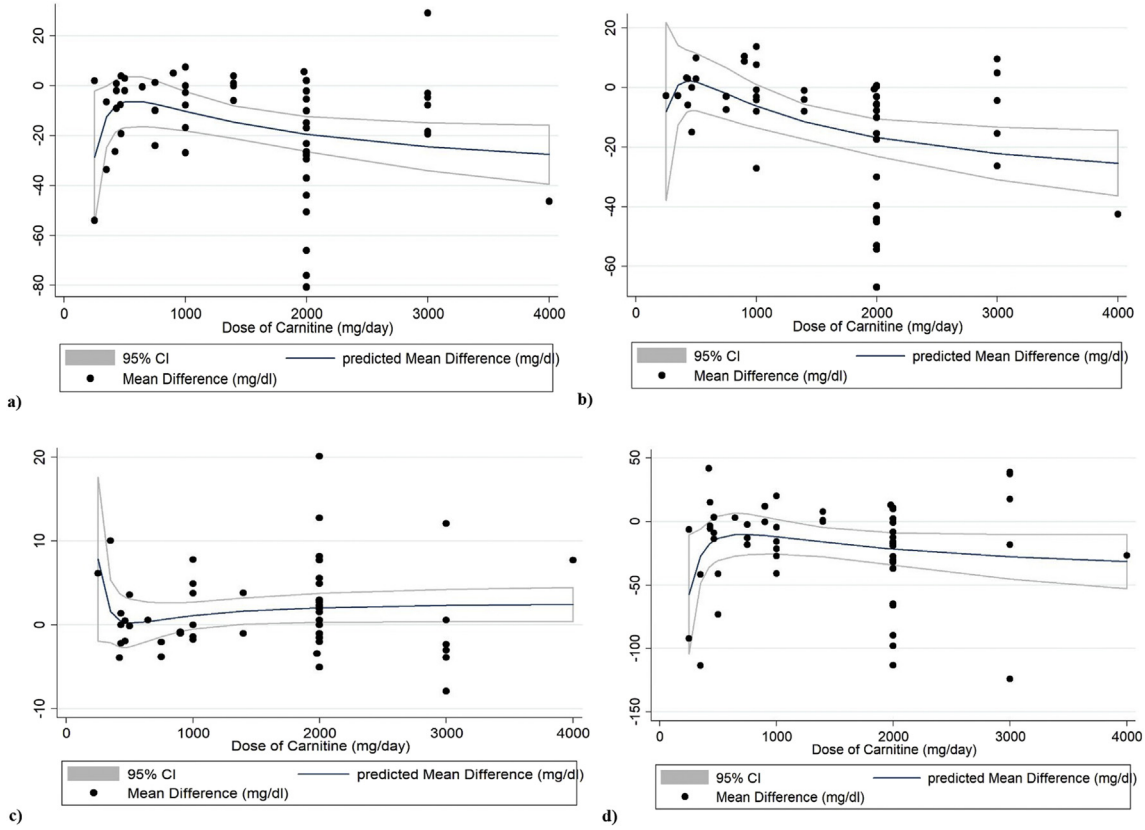

Figure 2 Non-linear dose-response relations between L-carnitine supplementation and absolute (unstandardized) mean differences. Dose-response relations between L-carnitine supplementation and absolute mean differences in a) TC (mg/dl- 56 trials), b) LDL-C (mg/dl - 47 trials), c) HDL-C (mg/dl - 51 trials) and d) TG (mg/dl −56 trials) based on dose of L-carnitine (mg/day) were depicted. L-carnitine supplementation did not change LDL-C (r = 18.87, P-nonlinearity = 0.057), HDL-C (r = −1.3, P-nonlinearity = 0.133), and TG (r = 29.69, P-nonlinearity = 0.089) based on L-carnitine dose in nonlinear fashion. However, L-carnitine supplementation did change TC in non-linear fashion. In that case LDL-C showed significant decreasing association (r = 21.11, P-nonlinearity = 0.036). The 95% CI is outlined between lines.

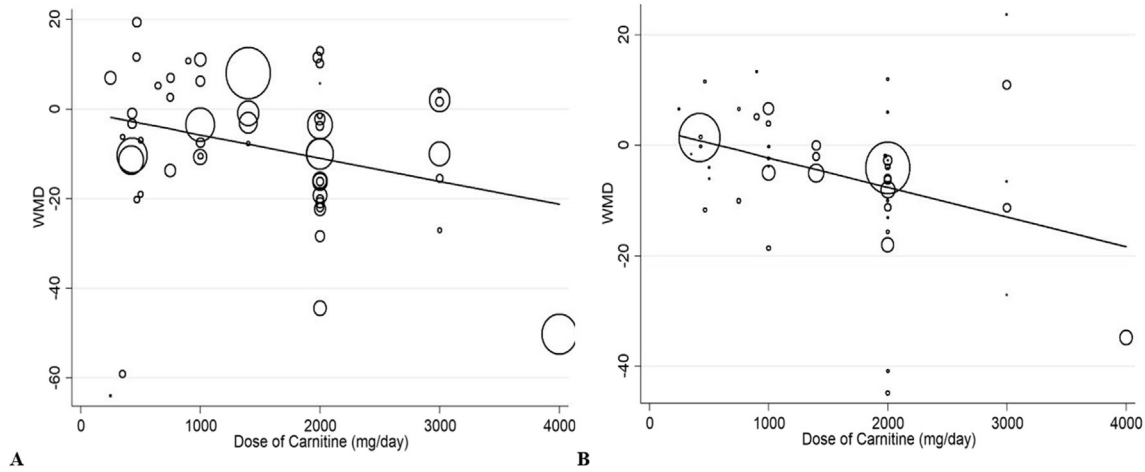

Figure 3 Random-effects meta-regression plots of the association between dose of L-carnitine (mg/day) and weighted mean difference of (A) TC, and (**B**) LDL-C, LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol.

response analyses, this was apparent for reduced TC, but no other components of the measured lipid profile. Although previous four meta-analyses had reported the effect of L-carnitine supplementation on lipid profile, they had mainly focused on patients with chronic kidney disease and diabetes [93,94,26,95]. Therefore, current meta-analysis is the first study summarizing publications on the effect of L-carnitine supplementation on lipid profile in

Table 3 Findings from meta-regression on the effects of carnitine supplementation on lipid profile by considering dose of carnitine.

	Effect sizes (n)	Beta	95% CI		I^2 residual	P-value
			Lower CI	Upper CI		
TC	56	−0.005	−0.009	−0.005	89.05	0.029*
LDL	47	−0.005	−0.009	−0.001	90.06	0.013*
HDL	51	0.0001	−0.0014	0.0016	92.21	0.868
TG	56	−0.0005	−0.01	0.009	90.27	0.910

either both healthy and unhealthy individuals. According to subgroup analysis L-carnitine supplementation when administered alone or combined with other lifestyle or drug administration lead to significant lowering effect on TC, TG and LDL-C and increasing effect on HDL-C.

Hyperlipidemia is a known feature for several metabolic diseases including metabolic syndrome, diabetes and CVD [96,97], for which several therapeutic strategies have been designed [98,9,8,13,7], with different chemical components like nutraceuticals and fibers. L-carnitine through its role in fatty acid beta-oxidation [99] which can reduce VLDL synthesis by increasing beta-oxidation and increased production of hepatic fatty acid binding proteins [28,29] may act as an adjuvant agent in the improvement of dyslipidemia. In the current meta-analysis, L-carnitine supplementation reduced serum concentrations of TC and LDL-C, in agreement with the previous meta-analysis in which reported beneficial effects of L-carnitine only in patients with diabetes [26]. As seen in our subgroup analysis, L-carnitine supplementation had beneficial effects for patients with diabetes/dyslipidemia.

In the current meta-analysis, we found a significant increase in HDL-C concentration following L-carnitine supplementation in all subgroups of health conditions. This is in accordance with previous meta-analysis which showed beneficial effect of oral L-carnitine supplementation on apolipoprotein-A1, the main apo-lipoprotein for HDL-C [26]. L-carnitine supplementation also lowered TG concentrations in both healthy individuals and those with hepatic disorders, but not in patients with diabetes/dyslipidemia and hemodialysis patients. Furthermore, pooled effect size from the present study showed L-carnitine did not affect TG concentrations in diabetic patients and patients under hemodialysis, as shown by Vidal-Casariego et al. [26]. Therefore, it seems that the effect of L-carnitine on TG depends on health condition of individuals. Moreover, as L-carnitine uptake by liver and muscle is controlled by insulin and glucagon through cellular transport processes [100,101] disrupted action of insulin in diabetes and diabetic hemodialysis patients could explain the lack of effect of L-carnitine supplementation.

We found a disparity in findings obtained from oral and intravenous supplementation of L-carnitine on lipid profile. One may conclude that L-carnitine dosage contributed for these different findings. As in most studies using oral supplements, participants received ≥2 g/d L-carnitine, while individuals with intravenous interventions received <2 g/d L-carnitine. Of course, subgroup analysis in present study showed that supplementation with ≥2 g/d L-carnitine was more effective than <2 g/d L-carnitine on lipid profiles. But it must be noted that absorption from oral L-carnitine supplements is substantially low; bioavailability of L-carnitine from oral supplements (500−6000 mg dosage) ranges from 14% to 18% of the total dose [102]. Nevertheless Sanchez-Niño et al. [103] raised a question for different effects of oral and intravenous L-carnitine on serum lipids: is the microbiota the answer? [103] Recent studies highlighted oral L-carnitine processing by gut microbiota to different metabolites which can influence L-carnitine absorption. In addition, suppression of intestinal resulted in higher circulating L-carnitine following oral supplementation [103]. The differential effect of oral versus intravenous L-carnitine supplementation may be related to gut microbiota; either higher final L-carnitine levels or reduced production of different metabolites.

Furthermore, in present study an intravenous form was only administered to hemodialysis patients. L-carnitine was ineffective on TC, LDL-C and TG in hemodialysis patients. Previous meta-analyses investigated both oral and intravenous L-carnitine supplementation in hemodialysis patients; there was no significant effect of L-carnitine supplementation on serum TC, HDL-C, VLDL-C and TG [94,93,95]; but showed significant lowering effect on LDL-C [94,93]. However, unlike our study, no significant effect of L-carnitine supplementation on HDL-C concentrations were found in previous meta-analysis [94,93]. This discrepancy between meta-analyses could be due to different number of published studies. In addition, differences in time of supplement administration between oral (daily) and intravenous (weekly) routes could explain the disparity. Although both intravenous and oral L-carnitine are approved in hemodialysis patients [104] but routine L-carnitine supplementation is not recommended by clinical guidelines in these patients [105−107].

Findings from meta-regression analysis also revealed that higher doses of L-carnitine had a greater lowering effect on LDL-C and TC, but not when administered at <2 g/d. Due to lack of included studies, L-carnitine did not show significant effect on TG and HDL-C when administered more than 6 months. Therefore, large scale dose-escalating trials are now needed before any firm conclusion could be drawn regrading intervention duration.

Some mechanisms have been reported for the beneficial effect of carnitine on lipid profile. Carnitine is involved in the mitochondrial transport of free fatty acid (FFA) and reduces FFA availability for triglycerides synthesis [108,94]. Carnitine enhances mitochondrial oxidation of long chain-FA, for which excess accumulation adversely affects insulin signaling and induces insulin resistance in muscle and heart [26,109], a well-known cause of hyperlipidemia [110]. Carnitine also stimulates the production of apolipoprotein-A1, the main apo-lipoprotein for HDL-C [26,111].

The strengths of our study is that we considered all published clinical trials conducted on the effect of L-carnitine supplementation on lipid profile. In addition, we considered all RCTs which were done on individuals with

different health conditions. However, some limitations should be considered, such as the different methods used for measuring lipid profile, considering lipid profile as a secondary outcome variable in a number of studies. Also the lack of controlling for baseline measures in some studies and different study designs should be taken into account.

Implications for practice

The evidence from this meta-analysis suggests that giving L-carnitine supplements to healthy and unhealthy subjects may have beneficial effects on the lipid profile.

Implications for research

Given that the currently available randomized trial data are heterogeneous, future large, long duration, high-quality trials should be designed to ensure low risk of bias and to meet current reporting standards for clinical trials. Daily dosing regimen ideally should be tailored to the individual to improve the evidence in this field. Several factors which can affect results, such as different dietary compliance, life style, absorption efficiency, production process, and geographical origin, also need to be considered. Another important point is that the maintenance beneficial effects of short and long-term and low and high-doses of L-carnitine to achieve improved lipid profile would be helpful.

Conclusion

L-carnitine supplementation, particularly in the form of oral supplements, had a beneficial effect on lipid profile. Moreover, this supplement was more effective in dose of $\geq$2 g/d L-carnitine. Additional well-designed RCTs recruiting a homogenous group of participants with a long period of intervention are required to further examine this subject.

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Author contribution

The authors' contribution was as follows: E.G.: contributed to the design and statistical analysis, E.G.: completely revised the article, A.H., M.A. and A.S. conducted the systematic search, screening and data extraction, M.S.: revised the manuscript for English, M.M. and O.S. prepared the primary manuscript, E.G. and M.S. finalized the manuscript, and all authors read and approved the final manuscript.

Conflicts of interest

All the authors declared that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.07.012.

References

[1] Hajar R. Framingham contribution to cardiovascular disease. Heart Views : Off J Gulf Heart Assoc 2016;17(2):78–81. https://doi.org/10.4103/1995-705x.185130.
[2] Asadi-Samani M, Bahmani M. Trends on the treatment of atherosclerosis; new improvements. Angiologica Persica Acta 2016;1(1).
[3] Nelson RH. Hyperlipidemia as a risk factor for cardiovascular disease. PrimaryCare 2013;40(1):195–211. https://doi.org/10.1016/j.pop.2012.11.003.
[4] Mann HD, Piotrowski P. Diet Modification for Hyperlipidemia: individual approach to diet planning and education. Can Fam Phys 1992;38:1483–9. Medecin de famille canadien.
[5] Ghaedi E, Kord-Varkaneh H, Mohammadi H, Askarpour M, Miraghajani M. Phytosterol supplementation could improve atherogenic and anti-atherogenic apolipoproteins: a systematic review and dose-response meta-analysis of randomized controlled trials. J Am Coll Nutr 2019:1–11. https://doi.org/10.1080/07315724.2019.1605313.
[6] Serban MC, Sahebkar A, Dragan S, Stoichescu-Hogea G, Ursoniu S, Andrica F, et al. A systematic review and meta-analysis of the impact of Spirulina supplementation on plasma lipid concentrations. Clinical Nutr (Edinburgh, Scotland) 2016;35(4):842–51. https://doi.org/10.1016/j.clnu.2015.09.007.
[7] Pirro M, Vetrani C, Bianchi C, Mannarino MR, Bernini F, Rivellese AA. Joint position statement on "Nutraceuticals for the treatment of hypercholesterolemia" of the Italian Society of Diabetology (SID) and of the Italian Society for the Study of Arteriosclerosis (SISA). Nutr Metab Cardiovas Dis – NMCD 2017;27(1):2–17. https://doi.org/10.1016/j.numecd.2016.11.122.
[8] Johnston TP, Korolenko TA, Pirro M, Sahebkar A. Preventing cardiovascular heart disease: promising nutraceutical and non-nutraceutical treatments for cholesterol management. Pharmacol Res 2017;120:219–25. https://doi.org/10.1016/j.phrs.2017.04.008.
[9] Bianconi V, Mannarino MR, Sahebkar A, Cosentino T, Pirro M. Cholesterol-lowering nutraceuticals affecting vascular function and cardiovascular disease risk. Curr Cardiol Rep 2018;20(7):53. https://doi.org/10.1007/s11886-018-0994-7.
[10] Hadi A, Arab A, Ghaedi E, Rafie N, Miraghajani M, Kafeshani M. Barberry (Berberis vulgaris L.) is a safe approach for management of lipid parameters: a systematic review and meta-analysis of randomized controlled trials. Complement Ther Med 2019;43:117–24. https://doi.org/10.1016/j.ctim.2019.01.017.
[11] Cicero AFG, Colletti A, Bajraktari G, Descamps O, Djuric DM, Ezhov M, et al. Lipid-lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. Nutr Rev 2017;75(9):731–67. https://doi.org/10.1093/nutrit/nux047.
[12] Cicero AFG, Colletti A. An update on the safety of nutraceuticals and effects on lipid parameters. Expert Opin Drug Saf 2018;17(3):303–13. https://doi.org/10.1080/14740338.2018.1429404.
[13] Pirro M, Mannarino MR, Bianconi V, Simental-Mendia LE, Bagaglia F, Mannarino E, et al. The effects of a nutraceutical combination on plasma lipids and glucose: a systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 2016;110:76–88. https://doi.org/10.1016/j.phrs.2016.04.021.
[14] Stanley CA. Carnitine deficiency disorders in children. Ann N Y Acad Sci 2004;1033:42–51. https://doi.org/10.1196/annals.1320.004.
[15] DARRYL C, noRoTEN M. Primary and secondary disorders of carnitine metabolism. Int Pediatr 1990;5(2):135.
[16] Broad E, Bolger C, Galloway S. Dietary carnitine intake and carnitine status in endurance-trained males. Nutr Diet 2006;63(3):148–54.

[17] Rebouche CJ. Carnitine function and requirements during the life cycle. FASEB J — Off Publ Fed Am Soc Exp Biol 1992;6(15):3379–86.
[18] Shang R, Sun Z, Li H. Effective dosing of L-carnitine in the secondary prevention of cardiovascular disease: a systematic review and meta-analysis. BMC Cardiovasc Disord 2014;14(1):88.
[19] Vaz FM, Wanders RJ. Carnitine biosynthesis in mammals. Biochem J 2002;361(Pt 3):417–29.
[20] Wang ZY, Liu YY, Liu GH, Lu HB, Mao CY. l-Carnitine and heart disease. Life Sci 2018;194:88–97. https://doi.org/10.1016/j.lfs.2017.12.015.
[21] Serban MC, Sahebkar A, Mikhailidis DP, Toth PP, Jones SR, Muntner P, et al. Impact of L-carnitine on plasma lipoprotein(a) concentrations: a systematic review and meta-analysis of randomized controlled trials. Sci Rep 2016;6:19188. https://doi.org/10.1038/srep19188.
[22] DiNicolantonio JJ, Lavie CJ, Fares H, Menezes AR, O'Keefe JH. L-carnitine in the secondary prevention of cardiovascular disease: systematic review and meta-analysis. Mayo Clin Proc 2013;88(6):544–51. https://doi.org/10.1016/j.mayocp.2013.02.007.
[23] Nazary-vannani A, Ghaedi E, Mousavi SM, Teymouri A, Rahmani J, Varkaneh HK. The effect of L-carnitine supplementation on serum leptin concentrations: a systematic review and meta-analysis of randomized controlled trials. In: Springer; 2018.
[24] Dastan F, Talasaz AH, Mojtahedzadeh M, Karimi A, Salehiomran A, Bina P, et al. Potential effect of L-carnitine on the prevention of myocardial injury after coronary artery bypass graft surgery. J Tehran Univ Heart Cent 2015;10(2):74.
[25] Montgomery SA, Thal LJ, Amrein R. Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. Int Clin Psychopharmacol 2003;18(2):61–71. https://doi.org/10.1097/01.yic.0000058280.28578.79.
[26] Vidal-Casariego A, Burgos-Pelaez R, Martinez-Faedo C, Calvo-Gracia F, Valero-Zanuy MA, Luengo-Perez LM, et al. Metabolic effects of L-carnitine on type 2 diabetes mellitus: systematic review and meta-analysis. Exp Clin Endocrinol Diabetes — Off J German Soc Endocrinol German Diabet Assoc 2013;121(4):234–8. https://doi.org/10.1055/s-0033-1333688.
[27] Fukami K, Yamagishi S-i, Sakai K, Nasu M, Okuda S. Effects of switching from oral administration to intravenous injection of L-carnitine on lipid metabolism in hemodialysis patients. Clin Kidney J 2014;7(5):470–4.
[28] Longo N, Frigeni M, Pasquali M. Carnitine transport and fatty acid oxidation. Biochim Biophys Acta 2016;1863(10):2422–35. https://doi.org/10.1016/j.bbamcr.2016.01.023.
[29] Kawano Y, Cohen DE. Mechanisms of hepatic triglyceride accumulation in non-alcoholic fatty liver disease. J Gastroenterol 2013;48(4):434–41.
[30] Vesela E, Racek J, Trefil L, Jankovy'ch V, Pojer M. Effect of L-carnitine supplementation in hemodialysis patients. Nephron 2001;88(3):218–23. https://doi.org/10.1159/000045993.
[31] Mitwalli AH, Al-Wakeel JS, Alam A, Tarif N, Abu-Aisha H, Rashed M, et al. L-carnitine supplementation in hemodialysis patients. Saudi J Kidney Dis Tanspl — Off Publ Saudi Cent Organ Transpl Saudi Arab 2005;16(1):17–22.
[32] Hakimi M, Sheikholeslami-Vatani D, Ali-Mohammadi M. EFFECT OF CONCURRENT TRAINING WITH INGESTED OF L-CARNITINE SUPPLEMENTATION ON HORMONAL CHANGES, LIPID PROFILE AND BODY COMPOSITION IN OBESE MEN. URMIAMJ 2015;26(3):185–93.
[33] Kudoh Y, Aoyama S, Torii T, Chen Q, Nagahara D, Sakata H, et al. The effects of oral L-carnitine supplementation on physical capacity and lipid metabolism in chronic hemodialysis patients. Nephron Extra 2014;4(1):33–41. https://doi.org/10.1159/000360086.
[34] Alavinejad P, Zakerkish M, Hajiani E, Hashemi SJ, Chobineh M, Moghaddam EK. Evaluation of L-carnitine efficacy in the treatment of non-alcoholic fatty liver disease among diabetic patients: a randomized double blind pilot study. J Gastroenterol Hepatol Res 2016;5(5):2191-2195. https://doi.org/10.17554/j.issn.2224-3992.2016.05.662.
[35] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151(4):264–9.
[36] Fedorov S. GetData Graph digitizer version 2.24. Available at: www.getdata-graph-digitizer.com; 2002.
[37] Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions, vol. 4. John Wiley & Sons; 2011.
[38] Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis. John Wiley & Sons; 2011.
[39] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ Br Med J (Clin Res Ed) 2003;327(7414):557.
[40] Mitchell MN. Interpreting and visualizing regression models using Stata, 005.369 M58. Stata Press College Station, TX; 2012.
[41] Tobias A. Assessing the influence of a single study in the meta-anyalysis estimate. Stat Tech Bull 1999;8(47).
[42] Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj 1997;315(7109):629–34.
[43] Bloomer RJ, Fisher-Wellman KH, Tucker PS. Effect of oral acetyl L-carnitine arginate on resting and postprandial blood biomarkers in pre-diabetics. Nutr Metab 2009;6. https://doi.org/10.1186/1743-7075-6-25.
[44] Brescia F, Balestra E, Iasella MG, Damato AB. Effects of combined treatment with simvastatin and L-carnitine on triglyceride levels in diabetic patients with hyperlipidaemia. Clin Drug Investig 2002;22:23–8. https://doi.org/10.2165/00044011-200222001-00004.
[45] Derosa G, Cicero AF, Gaddi A, Mugellini A, Ciccarelli L, Fogari R. The effect of L-carnitine on plasma lipoprotein(a) levels in hypercholesterolemic patients with type 2 diabetes mellitus. Clin Ther 2003;25(5):1429–39.
[46] Derosa G, Maffioli P, Ferrari I, D'Angelo A, Fogari E, Palumbo I, et al. Comparison between orlistat plus l-carnitine and orlistat alone on inflammation parameters in obese diabetic patients. Fundam Clin Pharmacol 2011;25(5):642–51. https://doi.org/10.1111/j.1472-8206.2010.00888.x.
[47] Derosa G, Maffioli P, Salvadeo SA, Ferrari I, Gravina A, Mereu R, et al. Effects of combination of sibutramine and L-carnitine compared with sibutramine monotherapy on inflammatory parameters in diabetic patients. Metab Clin Exp 2011;60(3):421–9. https://doi.org/10.1016/j.metabol.2010.03.010.
[48] El-sheikh HM, El-Haggar SM, Elbedewy TA. Comparative study to evaluate the effect of L-carnitine plus glimepiride versus glimepiride alone on insulin resistance in type 2 diabetic patients. Diabetes Metab Syndrome— Clin Res Rev 2019;13(1):167–73. https://doi.org/10.1016/j.dsx.2018.08.035.
[49] Galvano F, Li Volti G, Malaguarnera M, Avitabile T, Antic T, Vacante M, et al. Effects of simvastatin and carnitine versus simvastatin on lipoprotein(a) and apoprotein(a) in type 2 diabetes mellitus. Expert Opin Pharmacother 2009;10(12):1875–82. https://doi.org/10.1517/14656560903081745.
[50] Gonzalez-Ortiz M, Hernandez-Gonzalez SO, Hernandez-Salazar E, Martinez-Abundis E. Effect of oral L-carnitine administration on insulin sensitivity and lipid profile in type 2 diabetes mellitus patients. Ann Nutr Metabol 2008;52(4):335–8. https://doi.org/10.1159/000151488.
[51] Liang Y. The effects of oral L-carnitine treatment on blood lipid metabolism and the body fat content in the diabetic patient. Asia Pac J Clin Nutr 1998;7(2):192–5.
[52] Malaguarnera M, Vacante M, Avitabile T, Malaguarnera M, Cammalleri L, Motta M. L-Carnitine supplementation reduces oxidized LDL cholesterol in patients with diabetes. Am J Clin Nutr 2009;89(1):71–6. https://doi.org/10.3945/ajcn.2008.26251.
[53] Parvanova A, Trillini M, Podesta MA, Iliev IP, Aparicio C, Perna A, et al. Blood pressure and metabolic effects of acetyl-l-carnitine in type 2 diabetes: DIABASI randomized controlled trial. J Endocr Soc 2018;2(5):420–36. https://doi.org/10.1210/js.2017-00426.
[54] Rahbar AR, Shakerhosseini R, Saadat N, Taleban F, Pordal A, Gollestan B. Effect of L-carnitine on plasma glycemic and lipidemic profile in patients with type II diabetes mellitus. Eur J Clin Nutr 2005;59(4):592–6. https://doi.org/10.1038/sj.ejcn.1602109.
[55] Santo SS, Sergio N, Giuseppe M, Margherita F, Gea OC, Roberto F, et al. Effect of PLC on functional parameters and oxidative profile in type 2 diabetes-associated PAD. Diabetes Res Clin Pract 2006;72(3):231–7.
[56] Solfrizzi V, Capurso C, Colacicco AM, D'Introno A, Fontana C, Capurso SA, et al. Efficacy and tolerability of combined treatment with L-carnitine and simvastatin in lowering lipoprotein(a) serum levels in patients with type 2 diabetes mellitus. Atherosclerosis 2006;188(2):455–61. https://doi.org/10.1016/j.atherosclerosis.2005.11.024.

[57] Duranay M, Akay H, Yilmaz FM, Senes M, Tekeli N, Yucel D. Effects of L-carnitine infusions on inflammatory and nutritional markers in haemodialysis patients. Nephrol Dial Transplant – Off Publ Europ Dial Transpl Assoc - Europ Renal Assoc 2006;21(11):3211–4. https://doi.org/10.1093/ndt/gfl356.
[58] Emami Naini A, Moradi M, Mortazavi M, Amini Harandi A, Hadizadeh M, Shirani F, et al. Effects of oral L-carnitine supplementation on lipid profile, anemia, and quality of life in chronic renal disease patients under hemodialysis: a randomized, double-blinded, placebo-controlled trial. J Nutr Metab 2012;2012. https://doi.org/10.1155/2012/510483.
[59] Fukami K, Yamagishi S, Sakai K, Kaida Y, Adachi T, Ando R, et al. Potential inhibitory effects of L-carnitine supplementation on tissue advanced glycation end products in patients with hemodialysis. Rejuvenation Res 2013;16(6):460–6. https://doi.org/10.1089/rej.2013.1459.
[60] Golper TA, Wolfson M, Ahmad S, Hirschberg R, Kurtin P, Katz LA, et al. Multicenter trial of L-carnitine in maintenance hemodialysis patients. I. Carnitine concentrations and lipid effects. Kidney Int 1990;38(5):904–11. https://doi.org/10.1038/ki.1990.289.
[61] Higuchi T, Abe M, Yamazaki T, Mizuno M, Okawa E, Ando H, et al. Effects of levocarnitine on brachial-ankle pulse wave velocity in hemodialysis patients: a randomized controlled trial. Nutrients 2014;6(12):5992–6004. https://doi.org/10.3390/nu6125992.
[62] Higuchi T, Abe M, Yamazaki T, Okawa E, Ando H, Hotta S, et al. Levocarnitine improves cardiac function in hemodialysis patients with left ventricular hypertrophy: a randomized controlled trial. Am J Kidney Dis : Off J Natl Kidney Found 2016;67(2):260–70. https://doi.org/10.1053/j.ajkd.2015.09.010.
[63] Labonia WD. L-carnitine effects on anemia in hemodialyzed patients treated with erythropoietin. Am J Kidney Dis 1995;26(5):757–64.
[64] Mortazavi M, Seirafian S, Eshaghian A, Ghassami M, Taheri S, Atapour A, et al. Associations of oral L-carnitine with hemoglobin, lipid profile, and albumin in hemodialysis patients. J Res Med Sci 2012;17(1 SPL.1):S33–7.
[65] Sakurabayashi T, Miyazaki S, Yuasa Y, Sakai S, Suzuki M, Takahashi S, et al. L-carnitine supplementation decreases the left ventricular mass in patients undergoing hemodialysis. Circ J 2008;72(6):926–31.
[66] Shojaei M, Djalali M, Khatami M, Siassi F, Eshraghian M. Effects of carnitine and coenzyme Q10 on lipid profile and serum levels of lipoprotein (a) in maintenance hemodialysis patients on statin therapy. Iran J Kidney Dis 2011;5(2):114.
[67] Suchitra M, Ashalatha V, Sailaja E, Rao AM, Reddy VS, Bitla AR, et al. The effect of L-carnitine supplementation on lipid parameters, inflammatory and nutritional markers in maintenance hemodialysis patients. Saudi J Kidney Dis Tanspl 2011;22(6):1155.
[68] Eshghinia S, Marjani A, Kor BEZ. Effects of oral L-carnitine supplementation on lipid profiles and anemia in patients under hemodialysis in gonbadkavoos, Iran. Annu Res Rev Biol 2014;4(7):1092.
[69] Guarnieri G, Ranieri F, Toigo G, Vasile A, Ciman M, Rizzoli V, et al. Lipid-lowering effect of carnitine in chronically uremic patients treated with maintenance hemodialysis. Am J Clin Nutr 1980;33(7):1489–92.
[70] Nilsson-Ehle P, Cederblad G, Fagher B, Monti M, Thysell H. Plasma lipoproteins, liver function and glucose metabolism in haemodialysis patients: lack of effect of L-carnitine supplementation. Scand J Clin Lab Investig 1985;45(2):179–84.
[71] Rathod R, Baig M, Khandelwal P, Kulkarni S, Gade P, Siddiqui S. Results of a single blind, randomized, placebo-controlled clinical trial to study the effect of intravenous L-carnitine supplementation on health-related quality of life in Indian patients on. Indian J Med Sci 2006;60(4):143–53.
[72] Sohn HJ, Choi GB, Yoon KI. L-carnitine in maintenance hemodialysis clinical, lipid and biochemical effects. Korean J Nutr 1992;11(3):260–9.
[73] Steiber AL, Davis AT, Spry L, Strong J, Buss ML, Ratkiewicz MM, et al. Carnitine treatment improved quality-of-life measure in a sample of Midwestern hemodialysis patients. J Parenter Enteral Nutr 2006;30(1):10–5.
[74] Vaux E, Taylor D, Altmann P, Rajagopalan B, Graham K, Cooper R, et al. Effects of carnitine supplementation on muscle metabolism by the use of magnetic resonance spectroscopy and near-infrared spectroscopy in end-stage renal disease. Nephron Clin Pract 2004;97(2):c41–8.
[75] Vesela E, Racek J, Trefil L, Jankovy'ch V, Pojer M. Effect of L-carnitine supplementation in hemodialysis patients. Nephron 2001;88(3):218–23.
[76] Weschler A, Aviram M, Levin M, Better OS, Brook G. High dose of L-carnitine increases platelet aggregation and plasma triglyceride levels in uremic patients on hemodialysis. Nephron 1984;38(2):120–4.
[77] Yderstræde KB, Pedersen FB, Dragsholt C, Trostmann A, Laier E, Larsen H. The effect of L-carnitine on lipid metabolism in patients on chronic haemodialysis. Nephrol Dial Transplant 1987;1(4):238–41.
[78] Malaguarnera M, Maugeri D, Saraceno B, Romano M, Neri S, Rapisarda R, et al. Effects of carnitine on biochemical responses in patients with chronic hepatitis C treated with interferon-α. Clin Drug Investig 2002;22(7):443–8. https://doi.org/10.2165/00044011-200222070-00004.
[79] Romano M, Vacante M, Cristaldi E, Colonna V, Gargante MP, Cammalleri L, et al. L-Carnitine treatment reduces steatosis in patients with chronic hepatitis C treated with α-interferon and ribavirin. Dig Dis Sci 2008;53(4):1114–21.
[80] Florentin M, Elisaf MS, Rizos CV, Nikolaou V, Bilianou E, Pitsavos C, et al. L-carnitine/Simvastatin reduces lipoprotein (a) levels compared with simvastatin monotherapy: a randomized double-blind placebo-controlled study. Lipids 2017;52(1):1–9. https://doi.org/10.1007/s11745-016-4216-z.
[81] Hlais S, Reslan DRA, Sarieddine HK, Nasreddine L, Taan G, Azar S, et al. Effect of lysine, vitamin B6, and carnitine supplementation on the lipid profile of male patients with hypertriglyceridemia: a 12-week, open-label, randomized, placebo-controlled trial. Clin Ther 2012;34(8):1674–82. https://doi.org/10.1016/j.clinthera.2012.06.019.
[82] Malaguarnera M, Gargante MP, Russo C, Antic T, Vacante M, Malaguarnera M, et al. L-carnitine supplementation to diet: a new tool in treatment of nonalcoholic steatohepatitisa randomized and controlled clinical trial. Am J Gastroenterol 2010;105(6):1338–45. https://doi.org/10.1038/ajg.2009.719.
[83] Mahdavi R, Kolahi S, Attari VE, Mahdavi AM. L-carnitine supplementation ameliorates serum tumor necrosis factor-alpha and matrix metalloproteinase-3 in knee osteoarthritis women. Bangladesh J Pharmacol 2017;12(1):28–34. https://doi.org/10.3329/bjp.v12i1.30417.
[84] Mohammadi H, Djalali M, Daneshpazhooh M, Honarvar NM, Chams-Davatchi C, Sepandar F, et al. Effects of L-carnitine supplementation on biomarkers of oxidative stress, antioxidant capacity and lipid profile, in patients with pemphigus vulgaris: a randomized, double-blind, placebo-controlled trial. Eur J Clin Nutr 2017. https://doi.org/10.1038/ejcn.2017.131.
[85] Pistone G, Marino AD, Leotta C, Dell'Arte S, Finocchiaro G, Malaguarnera M. Levocarnitine administration in elderly subjects with rapid muscle fatigue. Drugs Aging 2003;20(10):761–7.
[86] Samimi M, Jamilian M, Ebrahimi FA, Rahimi M, Tajbakhsh B, Asemi Z. Oral carnitine supplementation reduces body weight and insulin resistance in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Clin Endocrinol 2016;84(6):851–7.
[87] Lee BJ, Lin JS, Lin YC, Lin PT. Effects of L-carnitine supplementation on lipid profiles in patients with coronary artery disease. Lipids Health Dis 2016;15:107. https://doi.org/10.1186/s12944-016-0277-5.
[88] Delaš I, Dražić T, Čačić-Hribljan M, Sanković K. Effect of L-carnitine supplementation on some biochemical parameters in blood serum of sedentary population. Croat Chem Acta 2008;81(1):163–8.
[89] Malaguarnera M, Cammalleri L, Gargante MP, Vacante M, Colonna V, Motta M. L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial. Am J Clin Nutr 2007;86(6):1738–44.
[90] Odo S, Tanabe K, Yamauchi M. A pilot clinical trial on l-carnitine supplementation in combination with motivation training: effects on weight management in healthy volunteers. Food Nutr Sci 2013;4(2):222.
[91] Karimi M, Rafraf M, Rashidi M, Jafari A. Effect of L-carnitine supplementation with or without moderate aerobic training on serum

lipid profile and body fat percentage in obese women. Iran J Endocrinol Metab 2013;14(5).
[92] Mosah HA, Khazaal FAK, Sahib HB, Hamdi AS. Effect of L-carnitine and raspberry ketones on metabolic parameters in Iraqi obese females, a comparative study. Int J Pharm Sci Rev Res 2015;31(2):63–8.
[93] Chen Y, Abbate M, Tang L, Cai G, Gong Z, Wei R, et al. L-Carnitine supplementation for adults with end-stage kidney disease requiring maintenance hemodialysis: a systematic review and meta-analysis. Am J Clin Nutr 2014;99(2):408–22. https://doi.org/10.3945/ajcn.113.062802.
[94] Huang H, Song L, Zhang H, Zhang H, Zhang J, Zhao W. Influence of L-carnitine supplementation on serum lipid profile in hemodialysis patients: a systematic review and meta-analysis. Kidney Blood Press Res 2013;38(1):31–41. https://doi.org/10.1159/000355751.
[95] Yang SK, Xiao L, Song PA, Xu X, Liu FY, Sun L. Effect of L-carnitine therapy on patients in maintenance hemodialysis: a systematic review and meta-analysis. J Nephrol 2014;27(3):317–29. https://doi.org/10.1007/s40620-013-0002-7.
[96] Kolovou G, Anagnostopoulou K, Cokkinos D. Pathophysiology of dyslipidaemia in the metabolic syndrome. Postgrad Med J 2005;81(956):358–66.
[97] Nelson RH. Hyperlipidemia as a risk factor for cardiovascular disease. Prim Care Clin Off Pract 2013;40(1):195–211.
[98] Hendrani AD, Adesiyun T, Quispe R, Jones SR, Stone NJ, Blumenthal RS, et al. Dyslipidemia management in primary prevention of cardiovascular disease: current guidelines and strategies. World J Cardiol 2016;8(2):201.
[99] Longo N, Frigeni M, Pasquali M. Carnitine transport and fatty acid oxidation. Biochim Biophys Acta Mol Cell Res 2016;1863(10):2422–35.
[100] Kispal G, Melegh B, Sandor A. Effect of insulin and glucagon on the uptake of carnitine by perfused rat liver. Biochim Biophys Acta 1987;929(2):226–8.
[101] Shannon CE, Nixon AV, Greenhaff PL, Stephens FB. Protein ingestion acutely inhibits insulin-stimulated muscle carnitine uptake in healthy young men. Am J Clin Nutr 2016;103(1):276–82. https://doi.org/10.3945/ajcn.115.119826.
[102] Rebouche CJ. Kinetics, pharmacokinetics, and regulation of L-carnitine and acetyl-L-carnitine metabolism. Ann N Y Acad Sci 2004;1033:30–41. https://doi.org/10.1196/annals.1320.003.
[103] Sanchez-Niño MD, Ortiz A. Differential effects of oral and intravenous l-carnitine on serum lipids: is the microbiota the answer? Oxford University Press; 2014.
[104] Medicare program; end-stage renal disease quality incentive program. Final rule. Fed Regist 2011;76(3):627–46.
[105] Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. Am J Kidney Dis : Off J Natl Kidney Found 2000;35(6 Suppl 2):S1–140.
[106] KDOQI clinical practice guideline for nutrition in children with CKD: 2008 update. Executive summary. Am J Kidney Dis – Off J Natl Kidney Found 2009;53(3 Suppl 2):S11–104. https://doi.org/10.1053/j.ajkd.2008.11.017.
[107] AHEMIÏ K. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int 2012;2:279.
[108] Naini AE, Sadeghi M, Mortazavi M, Moghadasi M, Harandi AA. Oral carnitine supplementation for dyslipidemia in chronic hemodialysis patients. Saudi J Kidney Dis Tanspl – Off Publ Saudi Cent Organ Transpl Saudi Arab 2012;23(3):484–8.
[109] Ringseis R, Keller J, Eder K. Role of carnitine in the regulation of glucose homeostasis and insulin sensitivity: evidence from in vivo and in vitro studies with carnitine supplementation and carnitine deficiency. Eur J Nutr 2012;51(1):1–18. https://doi.org/10.1007/s00394-011-0284-2.
[110] Entezari MH, Salehi M, Rafieian-Kopaei M, Kafeshani M. Fat and carbohydrate proportions influence on the insulin resistance; a systematic review and meta-analysis on controlled clinical trials. J Prev Epidemiol 2017;2(1).
[111] Baradaran A. The role of biomarkers to detect progression of diseases. Negat Results Clin Exp Stud 2017;1(1).