ABSTRACT

The findings of trials investigating the effect of L-carnitine administration on glycemic control are controversial. This meta-analysis of randomized controlled trials (RCTs) was performed to explore the effects of L-carnitine intake on glycemic control. Two authors independently searched electronic databases including MEDLINE, EMBASE, Cochrane Library, Web of Science, PubMed and Google scholar from 1990 until February 2019, in order to find relevant RCTs. 37 studies with 44 effect sizes met the inclusion criteria and were eligible for the meta-analysis. L-carnitine supplementation resulted in a significant reduction in fasting plasma glucose (FPG) (WMD: -4.57; 95 % CI: -6.88, -2.25), insulin (WMD: -1.21; 95 % CI: -1.85, -0.57), homeostatic model assessment for insulin resistance (HOMA-IR) (WMD: -0.67; 95 % CI: -0.90, -0.44) and HbA1C concentrations (WMD: -0.30; 95 % CI: -0.47, -0.13). L-Carnitine supplementation significantly reduced FPG, insulin, HOMA-IR, and HbA1c levels.

Keywords: L-carnitine, glycemic control, insulin resistance, meta-analysis

INTRODUCTION

There are many definitions of metabolic syndrome (MetS) but most of them include three of five cardiovascular disease (CVD) risk factors: hypertriglyceridemia, low levels of high density lipoprotein-cholesterol (HDL-C), abdominal obesity, hypertension, and hyperglycemia (Murthy et al., 2016). MetS is related with an increased risk of CVD, non-alcoholic fatty liver disease (NAFLD), type 2
diabetes mellitus (T2DM) and subsequent mortality (Ford, 2005; Gami et al., 2007; Tabák et al., 2009). As a consequence of lack of physical activity and excessive energy intake, MetS has become a disease which affects more than 25 % of the world population and causes serious concerns worldwide (Grundy, 2016). Insulin resistance and disturbed glucose metabolism resulting with hyperglycemia are most important in development of T2DM and other diseases related to MetS (Grundy et al., 2005).

Carnitine is a dipeptide which is an essential factor for the membrane transport of acyl-coenzyme A (CoA) (Suzuki et al., 1982). Carnitine deficiency reduces the use of lipids which causes serious metabolic defects (Takenaka et al., 2007). Many studies have found that treatment with carnitine has a substantial role in glucose tolerance, weight loss, fatty acids metabolism and insulin function (Molfino et al., 2010; Zhang et al., 2014). A relatively recently published meta-analysis by Xu et al. (2017), indicated that carnitine supplementation has beneficial effect in patients with insulin resistance. Several randomized controlled trials (RCTs) have investigated the efficacy of carnitine on markers related to glycemic control in patients with MetS, but their results are inconsistent. Alipour et al. (2014) reported that 8 weeks of carnitine supplementation in obese diabetic women on hypocaloric diet significantly reduced fasting glucose and insulin resistance. A 8-week carnitine supplementation in patients on peritoneal dialysis improved insulin sensitivity (Bonomini et al., 2013). It has also been shown that carnitine administration at a dosage of 2 g/day for 12 months to subjects with T2DM resulted in a significant improvement in homeostatic model assessment-insulin resistance (HOMA-IR) (Derosa et al., 2011). However, Shirali et al. (2016) indicated that L-carnitine plus caffeine in male teen soccer players increased their fasting glucose levels. Liang et al. (1998) suggested that 3 g/day carnitine supplementation during 12 weeks to non-insulin dependent diabetes mellitus patients had no effects on fasting glucose, HbA1c, and insulin levels. Discrepancies between the studies might be due to different concepts of studies as well as different formulations and dosages of carnitine used. The aim of this paper is to review systematically the trials investigating the effect of L-carnitine supplementation on glycemic control and to perform a meta-analysis in order to determine the effects of L-carnitine on markers related to glycemic control.

METHODS

Search strategy

Two authors independently searched electronic databases including MEDLINE, EMBASE, Cochrane Library, Web of Science, PubMed and Google scholar databases from 1990 until February 2019 for relevant RCTs investigating the association between L-carnitine intake and glycemic control. The search strategy was limited to RCTs conducted in English databases and performed in humans. The following MeSH and keywords were used to identify primary RCTs: intervention ("L-carnitine" OR "propionyl L-Carnitine" OR "Acetyl-L-carnitine" OR "carnitine orotate complex" OR "L-carnitine -L-tartrate" AND "supplementation" OR "intake"), and parameters ["fasting plasma glucose (FPG)" OR "insulin" OR "homeostasis model assessment of insulin resistance (HOMA-IR)" OR "HbA1C"]). The reference lists of related RCTs and previous reviews were hand-reviewed to detect further studies which were not captured in primary search.

Inclusion and exclusion criteria

RCTs fulfilling the following criteria were included in meta-analysis: trials on humans with cross-over design and/or either parallel, data analyzing the effect of L-carnitine on glycemic parameters extracted from RCTs with standard deviation (SD) and 95 % confidence interval (CI) for both treatment and control groups. Other studies such as in
vitro studies, animal experiments, observational studies, studies with duration below two weeks, case reports and studies without a control group were excluded from this meta-analysis.

**Data extraction and quality assessment**

Two authors independently (HF and AM) screened the articles based on the inclusion criteria. As the first step the title and abstract of studies were reviewed. Any disagreement was resolved by the judgment of the third author (ZA).

The following data were extracted from selected studies: year of publication, the first authors’ name, study location and design, dosage of intervention, sample size, duration of study, age of subjects, type of disease, the mean and SD for glycemic control in each treatment group. The quality of the selected RCTs was assessed by same authors independently using the Cochrane Collaboration risk of bias tool based on the following criteria: "allocation concealment, randomization generation, outcome assessors and blinding of participants, selective outcome reporting, incomplete outcome data, and other sources of bias".

**Data synthesis and statistical analysis**

Effects of L-carnitine on the changes of glycemic parameters. Weighted mean difference (WMD) with 95 % CI was used for pooling data to determine effect sizes. The random-effect model was used to report the pooled effect sizes using 95 % CI.

**Heterogeneity and publication bias**

Heterogeneity of included studies was evaluated using Cochrane’s Q test and I-square test. The funnel plot, as well as the Beggs’s and Egger’s regression tests was used to determine the publication bias. STATA 11.0 (StatCorp., College Station, TX) was applied for data analysis.

**RESULTS**

**Characteristics of included studies**

Diagram for study selection is shown in Figure 1. 37 studies with 44 effect sizes were included in this systematic review and meta-analysis (Table 1). The studies were published between 1998 and 2018. A total of 2467 subjects, including 1243 persons in intervention and 1224 persons in control groups, were recruited in these studies. Studies were done in China, Iran, Italy, India, USA, Japan, Mexico, UK, Lebanon, Korea, Spain, Egypt and Iraq. Studies used L-carnitine, propionyl L-carnitine, glycine propionyl L-carnitine, and acetyl L-carnitine for treatment. The dosages varied between 200 to 3,000 mg/day, with a duration range between 23 days and 12 months.

![Figure 1: Literature search and review flowchart for selection of studies](image-url)
### Table 1: Characteristics of included primary clinical trials

| Authors (Ref)          | Publication year | Country | Sample size (control/intervention) | Duration | Age (y) (intervention/control) | Intervention (type and dosage) |
|------------------------|------------------|---------|------------------------------------|----------|--------------------------------|--------------------------------|
| Liang et al.           | 1998             | China   | 23/23                              | 12 weeks | 59.4±1.17, 57.9±2.6             | 3000 mg L-carnitine            |
| Derosa et al.          | 2003             | Italy   | 48/46                              | 24 weeks | 52±6, 50±7                      | 2000 mg L-carnitine            |
| Rahbar et al.          | 2005             | Iran    | 16/19                              | 12 weeks | 50.5±4.8, 52.2±2.6              | 3000 mg L-carnitine            |
| Santo et al.           | 2006             | Italy   | 37/37                              | 12 months| 61.75±3.03, 61.26±1.6           | 2000 mg propionyl L-carnitine  |
| McMackin et al.        | 2007             | USA     | 36/36                              | 8 weeks  | ≥ 55                           | 500 mg acetyl-L-carnitine + 200 mg α-lipoic acid |
| Malaguarnera et al.    | 2007             | Italy   | 34/32                              | 24 weeks | 101±1.3, 101±1.4                | 2000 mg L-carnitine            |
| Morano et al.          | 2007             | Italy   | 8/8                                | 12 weeks | 45-70                          | 2000 mg propionyl L-carnitine  |
| Morano et al.          | 2007             | Italy   | 8/8                                | 12 weeks | 45-70                          | 2000 mg propionyl L-carnitine + sildenafil |
| Yonei et al.           | 2007             | Japan   | 17/18                              | 8 weeks  | 40-69                          | 200 mg L-carnitine + 700 conjugated linoleic acid |
| Santo et al.           | 2006             | Italy   | 37/37                              | 12 months| 61.75±3.03, 61.26±1.6           | 2000 mg propionyl L-carnitine  |
| Galvano et al.         | 2007             | Italy   | 34/32                              | 24 weeks | 47.9±5.4, 47.8±5.8              | 2000 mg L-carnitine + 20 mg simvastatin |
| Malaguarnera et al.    | 2007             | Italy   | 8/8                                | 12 weeks | 45-70                          | 2000 mg propionyl L-carnitine  |
| Bloomer et al.         | 2009             | USA     | 15/14                              | 8 weeks  | 31±11.22, 35±11.61             | 3000 mg acetyl-L-carnitine arginate |
| Bloomer et al.         | 2009             | Italy   | 10/4                               | 8 weeks  | 18-44                          | 1000 mg Glycine propionyl-L-carnitine |
| Bloomer et al.         | 2009             | Italy   | 11/5                               | 8 weeks  | 18-44                          | 3000 mg Glycine propionyl-L-carnitine |
| Derosa et al.          | 2010             | Italy   | 113/114                           | 12 months| 51±4, 53±6                     | 2000 mg L-carnitine + 360 mg orlistat |
| Malaguarnera et al.    | 2010             | Italy   | 38/36                              | 24 weeks | 47.9±5.4, 47.8±5.8              | 2000 mg L-carnitine + diet    |
| Derosa et al.          | 2010             | USA     | 110/113                           | 12 months| ≥18                            | 2000 mg L-carnitine + 10 mg sibutramine |
| Wall et al.            | 2011             | UK      | 7/7                                | 24 weeks | 27.1±5.8, 24.6±5.28             | 2720 mg L-carnitine + 160 g carbohydrate |
| Raffa et al.           | 2012             | Iran    | 11/11                              | 8 weeks  | 34.4±5.48, 36.5±7.33            | 2000 mg L-carnitine            |
| Raffa et al.           | 2012             | Iran    | 11/11                              | 8 weeks  | 34.8±6.25, 36.1±7.2             | 2000 mg L-carnitine + exercise |
| Hiais et al.           | 2012             | Lebanon | 19/15                              | 12 weeks | 55.6±1.70, 51.7±12.31           | 1000 mg L-carnitine            |
| Rondanelli et al.      | 2013             | Italy   | 45/41                              | 2 months | 25-45                          | 300 mg L-carnitine + Botanical extracts |
| Bonomini et al.        | 2013             | Italy   | 12/15                              | 120 days | ≥18                            | Glucose-based peritoneal dialysis solution enriched with L-carnitine (2000 mg/bag) |
| Hong et al.            | 2014             | Korea   | 24/24                              | 12 weeks | 30-75                          | 900 mg carnitine orotate complex + 750 mg metformin |
| Soare et al.           | 2014             | USA     | 26/28                              | 6 months | 38-55                          | 500 mg acetyl-L-carnitine + other substances |
| Alipour et al.         | 2014             | Iran    | 30/30                              | 8 weeks  | 20-50                          | 2000 mg L-carnitine + low calorie diet |
| Bañuls et al.          | 2015             | Spain   | 13/15                              | 12 weeks | 51.7±7.7                      | 2325 mg L-carnitine enriched bread + soluble fiber |
| Bañuls et al.          | 2015             | Spain   | 15/11                              | 12 weeks | 53.8±10.7                     | 2325 mg L-carnitine enriched bread + soluble fiber |
Table 1 (cont.): Characteristics of included primary clinical trials

| Authors (Ref) | Publication year | Country | Sample size (control/intervention) | Duration | Age (y) (intervention/control) | Intervention (type and dosage) |
|---------------|------------------|---------|-----------------------------------|----------|-------------------------------|--------------------------------|
| Bae et al.    | 2015             | Korea   | 39/39                             | 12 weeks | 20-70                         | 900 mg carnitine-orotate       |
| Mosah et al.  | 2015             | Iraq    | 18/18                             | 12 weeks | 33.11±6.53, 32.72±7.0         | 1000 mg L-carnitine           |
| Samimi et al. | 2016             | Iran    | 30/30                             | 12 weeks | 18-40                         | 250 mg carnitine              |
| Shirali et al.| 2016             | Iran    | 10/10                             | 8 weeks  | 16-18                         | 2000 mg L-carnitine + 6 mg/kg caffeine |
| Alavinejad et al. | 2016         | Iran    | 26/28                             | 12 weeks | 60±5, 59±9                    | 2250 mg L-carnitine           |
| An et al.     | 2016             | Korea   | 25/28                             | 12 weeks | 49.0±8.2, 50.9±9.1            | 1980 mg L-carnitine           |
| Akbarzadeh et al. | 2016          | Iran    | 22/22                             | 37 days  | 58.59±6.4, 55.21±8.3          | 3000 mg L-carnitine + other nutrients |
| Akbarzadeh et al. | 2016          | Iran    | 22/22                             | 23 days  | 58.72±8.5, 56.90±7.5          | 3000 mg L-carnitine + other nutrients |
| Ghorbani et al. | 2017           | Iran    | 10/10                             | 8 weeks  | 52.7±6.1                      | 500 mg L-carnitine three times a week + exercise |
| Ghorbani et al. | 2017           | Iran    | 10/10                             | 8 weeks  | 52.7±6.1                      | 500 mg L-carnitine three times a week + 2000 mg omega 3 + exercise |
| Ghorbani et al. | 2017           | Iran    | 10/10                             | 8 weeks  | 52.7±6.1                      | 500 mg L-carnitine three times a week + 2000 mg omega 3 |
| Parvanova et al. | 2018          | Italy   | 110/109                           | 24 weeks | >40                           | 2000 mg acetyl L-carnitine + 10 to 20 mg simvastatin |
| El-sheikh et al. | 2019           | Egypt   | 27/31                             | 24 weeks | 59±8.6, 53±8.8                | 2000 mg L-carnitine + 4 mg glimepiride |
The effects of L-carnitine supplementation on FPG

Pooling 44 effect sizes from 37 studies, a significant reduction was found in FPG following L-carnitine supplementation (WMD): -4.57; 95 % CI: -6.88, -2.25) (Table 2 and Figure 2A). This finding remained unchanged in most subgroup analyses. However, it became non-significant in studies done on participants aged <45 years (WMD: -0.55; 95 % CI: -1.43, 0.33), studies used L-carnitine in dosages of 1,000-2,000 mg/day (WMD: -0.24; 95 % CI: -1.53, 2.00), and those with a duration of 3-6 months (WMD: -0.20; 95 % CI: -0.76, 0.37), as well as studies done in healthy persons (WMD: -0.29; 95 % CI: -1.16, 0.59). A significant increase in FPG was found in two available studies on patients with renal diseases (WMD: 0.63; 95 % CI: 0.00, 1.27) (Table 3).

Table 2: The effects of carnitine supplementation on glycemic control

| VARIABLES | NUMBER OF EFFECT SIZES | WEIGHTED MEAN DIFFERENCE | CI 95 % | HETEROGENEITY | I² (%) | P-value heterogeneity |
|-----------|------------------------|--------------------------|--------|----------------|--------|----------------------|
| FPG       | 44                     | -4.57                    | -6.88, -2.25 | 95.7          | <0.001 |
| INSULIN   | 25                     | -1.21                    | -1.85, -0.57 | 89.8          | <0.001 |
| HOMA-IR   | 21                     | -0.67                    | -0.90, -0.44 | 91.5          | <0.001 |
| HBA1C     | 26                     | -0.30                    | -0.47, -0.13 | 92.1          | <0.001 |

FPG: Fasting Plasma Glucose; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; HbA1c: Hemoglobin A1C

Figure 2A: FPG
Figure 2B: Insulin

| Study ID | WMD (95% CI) | % Weight |
|----------|--------------|----------|
| Bloomer R (2009) | -0.50 (-2.26, 1.26) | 1.38 |
| Derosa G (2010) | -0.90 (-1.52, -0.28) | 4.93 |
| Malaguernera M (2010) | -0.92 (-1.08, -0.78) | 7.50 |
| Derosa G (2010) | -0.80 (-1.49, -0.11) | 4.55 |
| Raafat M (a) (2012) | -0.99 (-1.47, -0.51) | 5.77 |
| Raafat M (b) (2012) | -0.80 (-1.51, -0.09) | 4.42 |
| Rondanelli M (2013) | -0.40 (-0.46, -0.34) | 7.69 |
| Hong E (2014) | -0.60 (-4.09, 2.89) | 0.41 |
| Soare A (2014) | 0.07 (-0.07, 0.21) | 7.51 |
| Alipour B (2014) | -0.23 (-0.35, -0.11) | 7.55 |
| Banuls C (a) (2015) | 0.07 (-0.48, 0.62) | 5.34 |
| Banuls C (b) (2015) | -0.80 (-1.45, -0.15) | 4.77 |
| Bae J (2015) | -0.03 (-2.09, 2.63) | 0.68 |
| Sanimi M (2016) | -0.72 (-1.35, -0.09) | 4.87 |
| Akbarzadeh M (a) (2016) | -0.69 (-1.13, -0.25) | 5.98 |
| Akbarzadeh M (b) (2016) | -0.59 (-1.12, 0.06) | 5.44 |
| Ghorbani M (a) (2017) | 0.64 (-0.21, 1.49) | 3.74 |
| Ghorbani M (b) (2017) | 0.08 (-1.15, 1.31) | 2.38 |
| Ghorbani M (c) (2017) | -2.11 (-2.94, -1.28) | 3.83 |
| Parwanova A (2018) | -0.10 (0.42, 0.22) | 6.70 |
| El-sheikh H (2019) | -3.70 (-4.39, -3.01) | 4.56 |
| Overall (I-squared = 91.5%, p = 0.000) | -0.67 (-0.90, -0.44) | 100.00 |

NOTE: Weights are from random effects analysis

Figure 2C: HOMA-IR

| Study ID | WMD (95% CI) | % Weight |
|----------|--------------|----------|
| Bloomer R (2009) | -0.80 (-2.03, 0.43) | 5.00 |
| Derosa G (2007) | 1.90 (-0.21, 4.01) | 3.69 |
| Yonei Y (2007) | -0.66 (-5.48, 4.16) | 1.38 |
| Bloomer R (2009) | 1.84 (-0.25, 3.93) | 3.71 |
| Derosa G (2010) | -1.00 (-3.49, 1.49) | 3.19 |
| Malaguernera M (2010) | -1.70 (-2.80, -0.60) | 5.20 |
| Derosa G (2010) | -1.20 (-2.14, -0.26) | 5.42 |
| Wall B (2011) | 1.00 (0.51, 1.49) | 5.91 |
| Raafat M (a) (2012) | -2.40 (-3.76, -1.04) | 4.80 |
| Raafat M (b) (2012) | -3.05 (-5.34, -0.76) | 3.45 |
| Rondanelli M (2013) | -0.23 (-0.27, -0.20) | 6.13 |
| Bonomini M (2013) | -7.00 (-13.92, -0.08) | 0.76 |
| Hong E (2014) | -1.70 (-11.79, 8.39) | 0.38 |
| Soare A (2014) | 0.20 (-0.51, 0.91) | 5.70 |
| Banuls C (a) (2015) | 0.76 (-1.22, 2.74) | 3.87 |
| Banuls C (b) (2015) | -2.31 (-4.44, -0.18) | 3.66 |
| Samimi M (2016) | -3.13 (-5.46, -0.80) | 3.49 |
| Akbarzadeh M (a) (2016) | -3.54 (-6.38, -0.70) | 2.79 |
| Akbarzadeh M (b) (2016) | -1.73 (-3.49, 0.03) | 4.20 |
| Ghorbani M (a) (2017) | 1.62 (-0.20, 3.44) | 4.10 |
| Ghorbani M (b) (2017) | 0.27 (-2.38, 2.92) | 3.00 |
| Ghorbani M (c) (2017) | -4.79 (-6.60, -2.98) | 4.12 |
| Parwanova A (2018) | -0.50 (-1.39, 0.39) | 5.48 |
| El-sheikh H (2019) | -7.05 (-8.28, -5.82) | 5.01 |
| Overall (I-squared = 89.8%, p = 0.000) | -1.21 (-1.85, -0.57) | 100.00 |

NOTE: Weights are from random effects analysis
Figure 2A-D: Meta-analysis of glycemic control weighted mean difference estimates for A) FPG, B) insulin, C) HOMA-IR, D) HbA1c in the L-carnitine supplements and placebo groups (CI=95 %). Different capital letters indicate various dosage of L-carnitine used and different phases of L-carnitine treatment.

Table 3: Subgroup analyses for the effects of carnitine supplementation on glycemic control

| VARIABLES                      | SUBGROUPS                  | NUMBER OF EFFECT SIZES | POOLED WMD | 95 % CI       | (%) |
|--------------------------------|----------------------------|------------------------|------------|---------------|-----|
| FPG                            | Participants’ age           | <45 year               | 15         | -0.55         | -1.43, 0.33 | 80.3 |
|                                |                            | ≥45 year               | 29         | -3.36         | -3.81, -2.92 | 96.9 |
| Supplement dosage              | <1000 mg/day               | 13                     | -6.85      | -7.59, -6.11  | 97.5 |
|                                | 1000-2000 mg/day           | 3                      | 0.24       | -1.53, 2.00   | 0.06 |
|                                | ≥2000 mg/day               | 28                     | -1.26      | -1.75, -0.77  | 92.8 |
| Study duration                 | <3 month                   | 17                     | -3.67      | -7.07, -5.68  | 96.7 |
|                                | 3-6 month                  | 16                     | -0.20      | -0.76, 0.37   | 88.3 |
|                                | 6-12 month                 | 7                      | -1.79      | -2.83, -0.75  | 95.6 |
|                                | ≥12 month                  | 4                      | -10.80     | -13.01, -8.59 | 83.6 |
| Study sample size              | <50                        | 25                     | -4.36      | -4.96, -3.77  | 96.2 |
|                                | 50-100                     | 16                     | -0.95      | -1.51, -0.39  | 94.0 |
|                                | ≥100                       | 3                      | -8.59      | -10.64, -6.54 | 94.7 |
| Study location                 | Eastern countries          | 20                     | -5.75      | -6.42, -5.08  | 96.4 |
|                                | Western countries          | 24                     | -1.17      | -1.67, -0.68  | 93.7 |
| Participants’ health condition | Healthy                    | 14                     | -0.29      | -1.16, 0.59   | 77.3 |
|                                | Renal disease              | 2                      | 0.63       | 0.00, 1.27    | 75.0 |
|                                | Chronic metabolic diseases | 22                     | -7.97      | -8.66, -7.27  | 96.0 |
|                                | Cardiovascular disease     | 3                      | -4.34      | -7.46, -1.22  | 0.00 |
|                                | Liver disease              | 2                      | -12.74     | -15.25, -10.24| 71.1 |
|                                | Other diseases             | 1                      | 0.90       | -1.49, 3.29   | -   |
Table 3 (cont.): Subgroup analyses for the effects of carnitine supplementation on glycemic control

| VARIABLES                        | SUBGROUPS                  | NUMBER OF EFFECT SIZES | POOLED WMD | 95 % CI       | \( I^2 (% \) |
|----------------------------------|----------------------------|-------------------------|------------|---------------|----------------|
| **INSULIN**                      |                            |                         |            |               |                |
| Participants’ age                | <45 year                   | 10                      | -0.23      | -0.26, -0.20  | 84.7           |
|                                  | ≥45 year                   | 15                      | -1.52      | -1.90, -1.15  | 89.2           |
| Study sample size                | <50                        | 15                      | 0.01       | -0.37, 0.39   | 83.9           |
|                                  | 50-100                     | 7                       | -0.24      | -0.27, -0.21  | 95.6           |
|                                  | ≥100                       | 3                       | -0.91      | -1.39, -0.42  | 0.0            |
| Study location                   | Eastern countries          | 11                      | -1.68      | -2.33, -1.03  | 76.5           |
|                                  | Western countries          | 14                      | -0.24      | -0.27, -0.21  | 92.5           |
| Supplement dosage                | <1000 mg/day               | 10                      | -0.23      | -0.27, -0.20  | 79.4           |
|                                  | ≥1000 mg/day               | 15                      | -0.80      | -1.08, -0.51  | 92.1           |
| Study duration                   | <3 month                   | 12                      | -0.24      | -0.27, -0.21  | 81.7           |
|                                  | 3-6 month                  | 5                       | -1.53      | -2.73, -0.32  | 59.4           |
|                                  | 6-12 month                 | 6                       | -0.28      | -0.61, 0.04   | 96.7           |
|                                  | ≥12 month                  | 2                       | -1.08      | -1.66, -0.50  | 0.0            |
| Participants’ health condition   | Healthy                    | 9                       | -0.23      | -0.26, -0.20  | 83.7           |
|                                  | Renal disease              | 1                       | -7.00      | -13.92, -0.08 | -              |
|                                  | Chronic metabolic diseases | 10                      | -1.54      | -1.92, -1.15  | 92.5           |
|                                  | Cardiovascular disease     | 3                       | -0.85      | -2.07, 0.37   | 81.7           |
|                                  | Liver disease              | 2                       | -1.70      | -2.79, -0.61  | 0.0            |
| HOMA-IR                          |                            |                         |            |               |                |
| Participants’ age                | <45 year                   | 8                       | -0.33      | -0.38, -0.28  | 86.5           |
|                                  | ≥45 year                   | 13                      | -0.81      | -0.92, -0.70  | 90.2           |
| Study sample size                | <50                        | 11                      | -0.63      | -0.83, -0.43  | 67.8           |
|                                  | 50-100                     | 7                       | -0.40      | -0.44, -0.35  | 96.9           |
|                                  | ≥100                       | 3                       | -0.35      | -0.61, -0.08  | 71.4           |
| Study location                   | Eastern countries          | 11                      | -0.35      | -0.46, -0.25  | 74.6           |
|                                  | Western countries          | 10                      | -0.42      | -0.46, -0.37  | 95.4           |
| Participants’ health condition   | Healthy                    | 6                       | -0.35      | -0.40, -0.30  | 89.5           |
|                                  | Chronic metabolic diseases | 11                      | -0.35      | -0.45, -0.24  | 92.2           |
|                                  | Cardiovascular disease     | 2                       | -0.65      | -0.99, -0.31  | 0.0            |
|                                  | Liver disease              | 2                       | -0.92      | -1.06, -0.78  | 0.0            |
| Supplement dosage                | <2000 mg/day               | 8                       | -0.34      | -0.39, -0.29  | 88.6           |
|                                  | ≥2000 mg/day               | 13                      | -0.57      | -0.65, -0.49  | 92.1           |
| Study duration                   | <3 month                   | 10                      | -0.39      | -0.44, -0.34  | 76.8           |
|                                  | 3-6 month                  | 5                       | -0.42      | -0.76, -0.07  | 25.0           |
|                                  | 6-12 month                 | 4                       | -0.45      | -0.55, -0.36  | 98.4           |
|                                  | ≥12 month                  | 2                       | -0.86      | -1.32, -0.39  | 0.0            |
| HBA1C                            |                            |                         |            |               |                |
| Participants’ age                | <45 year                   | 3                       | -0.12      | -0.24, -0.01  | 94.5           |
|                                  | ≥45 year                   | 23                      | -0.19      | -0.24, -0.15  | 92.1           |
| Supplement dosage                | <2000 mg/day               | 9                       | -0.19      | -0.28, -0.11  | 86.4           |
|                                  | ≥2000 mg/day               | 17                      | -0.22      | -0.28, -0.17  | 93.7           |
| Study location                   | Eastern countries          | 11                      | -0.10      | -0.16, -0.05  | 85.1           |
|                                  | Western countries          | 10                      | -0.30      | -0.37, -0.24  | 95.4           |
| Study duration                   | <3 month                   | 9                       | -0.12      | -0.19, -0.06  | 67.3           |
|                                  | 3-6 month                  | 10                      | -0.17      | -0.23, -0.10  | 82.2           |
|                                  | 6-12 month                 | 3                       | -0.23      | -0.34, -0.13  | 98.9           |
|                                  | ≥12 month                  | 4                       | -0.78      | -0.99, -0.57  | 81.0           |
| Study sample size                | <50                        | 14                      | -0.13      | -0.19, -0.07  | 63.1           |
|                                  | 50-100                     | 9                       | -0.22      | -0.28, -0.16  | 96.4           |
|                                  | ≥100                       | 3                       | -0.24      | -0.36, -0.11  | 96.4           |

FPG: Fasting Plasma Glucose; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; HbA1c: Hemoglobin A1C
The effects of L-carnitine supplementation on insulin levels

Combining 25 effect sizes from 20 studies, we found a significant reductive effect of L-carnitine supplementation on insulin levels (WMD: -1.21; 95% CI: -1.85, -0.57) (Table 2 and Figure 2B). No significant changes in insulin concentrations were found in studies which enrolled <50 subjects (WMD: 0.01; 95% CI: -0.37, 0.39), studies with a duration of 6–12 months (WMD: -0.28; 95% CI: -0.61, 0.04), and those done on patients with CVD (WMD: -0.85; 95% CI: -2.07, 0.37) (Table 3).

The effects of L-carnitine supplementation on HOMA-IR

The pooled analysis of data from 16 studies with 21 effect sizes showed a significant reduction in HOMA-IR following intake of L-carnitine supplements (WMD: -0.67; 95% CI: -0.90, -0.44) (Table 2 and Figure 2C). This finding remained unchanged in all subgroup analyses (Table 3).

The effects of L-carnitine supplementation on HbA1C

L-carnitine supplementation resulted in a significant reduction in HbA1C concentrations, when we combined data from 22 studies with 26 effect sizes (WMD: -0.30; 95% CI: -0.47, -0.13) (Table 2 and Figure 2D). This finding did not change through subgroup analyses (Table 3).

DISCUSSION

This is the first meta-analysis of RCTs analyzing the effect of carnitine supplementation on glucose homeostasis parameters. In the present study, we showed that carnitine supplementation can significantly reduce FPG, insulin, HOMA-IR, and HbA1c levels.

Previous evidence suggested that carnitine might have a positive impact on glycemic control. A meta-analysis by Xu et al. (Xu et al., 2017) indicated that carnitine supplementation had beneficial effects on HOMA-IR score. Supplementation with carnitine at a dosage of 2 g/day for 4 weeks in patients with impaired glucose metabolism was associated with a significant reduction of insulin levels and HOMA-IR score. In a trial by Bae et al. (2015), carnitine supplementation resulted with a significant decrease in fasting glucose, HbA1c, and HOMA-IR score. Opposite findings were also reported. For example, Liang et al. (1998) were unable to find any significant effects of carnitine on FPG, HbA1c, or insulin levels.

Different dosages of carnitine, different types of carnitine as well as the use of only carnitine or carnitine combined with other supplements, heterogeneity in design of studies, and differences in populations involved in studies are some of the possible reasons that may explain different results. When patients with T2DM have other risk factors, particularly components of MetS, they are at especially high risk for CVD (Grundy et al., 2004). In order to prevent CVD, control of blood glucose and other CVD risk factors in these patients is very important (Gæde et al., 2003). Due to changed insulin secretion and pancreatic beta cell function normal glucose equilibrium is in this condition impaired (Xia et al., 2012). Several mechanisms have been suggested as possible explanations for beneficial effects of carnitine on fasting glucose and insulin resistance. Increasing mitochondrial oxidation of long-chain acyl-CoAs is one of important mechanisms by which carnitine could improve glycemic control (Kerner and Hoppel, 2000; McGarry and Brown, 1997). It has been shown that carnitine supplementation reduces oxidative stress in diabetic patients (Malaguarnera et al., 2009a). Carnitine supplementation may have beneficial effects on glucose homeostasis also by modulating the expression of genes involved in insulin signaling pathway, changing the expression of gluconeogenic and glycolytic enzymes, regulating the intra-mitochondrial acyl-CoA/CoA ratio, and modulating the activity of pyruvate dehydrogenase complex (Steiber et al., 2004).
CONCLUSIONS
This meta-analysis has shown that L-carnitine supplementation significantly reduces FPG, insulin, HOMA-IR, and HbA1c levels.

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Competing interests
The authors declare no conflict of interest.

REFERENCES
Akbarzadeh M, Eftekhari MH, Shafa M, Alipour S, Hassanzadeh J. Effects of a new metabolic conditioning supplement on perioperative metabolic stress and clinical outcomes: a randomized, placebo-controlled trial. Iran Red Crescent Med J. 2016;18:e26207.

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;5:2191-5.

Alipour B, Barzegar A, Panahi F, Saafaeian A, Eshaghi M. Effect of L-carnitine supplementation on metabolic status in obese diabetic women with hypocaloric diet. Health Scope. 2014;3:e14615.

An JH, Kim YJ, Kim KJ, Kim NH, Kim HY, et al. L-carnitine supplementation for the management of fatigue in patients with hypothyroidism on levothyroxine treatment: a randomized, double-blind, placebo-controlled trial. Endocr J. 2016;63:885-95.

Bae JC, Lee WY, Yoon KH, Park JY, Son HS, Han KA, et al. Improvement of nonalcoholic fatty liver disease with Carnitine-Orotate Complex in Type 2 Diabetes (CORONA): a randomized controlled trial. Diabetes Care. 2015;38:1245-52.

Bañuls C, Rovira-Llopis S, Monzó N, Solá E, Viadel B, Víctor VM, et al. The consumption of a bread enriched with dietary fiber and L-carnitine improves glucose homeostasis and insulin sensitivity in patients with metabolic syndrome. J Cereal Sci. 2015;64:159-67.

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 (Lond). 2009;6:25.

Bloomer RJ, Tschume LC, Smith WA. Glycine propionyl-L-carnitine modulates lipid peroxidation and nitric oxide in human subjects. Int J Vitamin Nutr Res. 2009b;79:131-41.

Bonomini M, Di Liberato L, Del Rosso G, Stingone A, Marinangeli G, Consoli A, et al. Effect of an L-carnitine–containing peritoneal dialysate on insulin sensitivity in patients treated with CAPD: a 4-month, prospective, multicenter randomized trial. Am J Kidney Dis. 2013;62:929-38.

Deroga 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;25:1429-39.

Deroga G, Maffioli P, Ferrari I, D’Angelo A, Fogari E, Palumbo I, et al. Orlistat and L-carnitine compared to orlistat alone on insulin resistance in obese diabetic patients. Endocr J. 2010a;57:777-86.

Deroga G, Maffioli P, Salvadeo SA, Ferrari I, Gravina A, Mereu R, et al. Sibutramine and L-carnitine compared to sibutramine alone on insulin resistance in diabetic patients. Intern Med. 2010b;49:1717-25.

Deroga 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. Metabolism. 2011;60:421-9.

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 Syndr. 2019;13:167-73.

Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. Diabetes Care. 2005;28:1769-78.

Gæde P, Vedel P, Larsen N, Jensen GV, Parving H-H, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med. 2003;348:383-93.

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 apo-protein (a) in type 2 diabetes mellitus. Exp Opin Pharmacother. 2009;10:1875-82.

Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol. 2007;49:403-14.
Ghorbani M, Hassani A, Donyai A, Qadiri M. The effect of 8-weeks compound exercises training with omega-3 and l-carnitine supplementation intake on serum levels of visfatin in type 2 diabetic women. Iran J Endocrinol Metab. 2017;19:18-25.

González-Ortiz M, Hernández-González SO, Hernández-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 Metab. 2008;52:335-8.

Grundy SM. Metabolic syndrome update. Trends Cardiovasc Med. 2016;26:364-73.

Grundy SM, Cleeman JI, Merz CNB, Brewer HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. J Am Coll Cardiol. 2004;44:720-32.

Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation. 2005;112:2735-52.

Hlais S, Reslan DRA, Sari eddine 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;34:1674-82.

Hong ES, Kim EK, Kang SM, Khang AR, Choi SH, Park KS, et al. Effect of carnitine-orotate complex on glucose metabolism and fatty liver: A double-blind, placebo-controlled study. Clin Ther. 2012;34:1449-57.

Kerner J, Hoppel C. Fatty acid import into mitochondria. Biochim Biophys Acta. 2000;1486:1-17.

Liang Y, Li Y, Shan J, Yu B, Ho Z. 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;7:192-5.

Malaguarnera M, Campmalleri 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;86:1738-44.

Malaguarnera M, Vacante M, Avitabile T, Malaguarnera M, Campmalleri L, Motta M. L-Carnitine supplementation reduces oxidized LDL cholesterol in patients with diabetes. Am J Clin Nutr. 2009a;89:71-6.

Malaguarnera M, Vacante M, Motta M, Malaguarnera M, Li Volti G, Galvano F. Effect of L-carnitine on the size of low-density lipoprotein particles in type 2 diabetes mellitus patients treated with simvastatin. Metabolism. 2009b;58:1618-23.

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 steatohepatitis - a randomized and controlled clinical trial. Am J Gastroenterol. 2010;105:1338-45.

McGarry JD, Brown NF. The mitochondrial carnitine palmitoyltransferase system - from concept to molecular analysis. Eur J Biochem. 1997;244:1-14.

McMackin CJ, Widlansky ME, Hamburg NM, Huang AL, Weller S, Holbrook M, et al. Effect of combined treatment with α-lipoic acid and acetyl-l-carnitine on vascular function and blood pressure in patients with coronary artery disease. J Clin Hypertens (Greenwich). 2007;9:249-55.

Molfino A, Cascino A, Conte C, Ramaccini C, Fanelli FR, Laviano A. Caloric restriction and L-carnitine administration improves insulin sensitivity in patients with impaired glucose metabolism. JPEN J Parenter Enteral Nutr. 2010;34:295-9.

Morano S, Mandosi E, Fallarino M, Gatti A, Tiberti C, Sensi M, et al. Antioxidant treatment associated with sildenafil reduces monocyte activation and markers of endothelial damage in patients with diabetic erectile dysfunction: a double-blind, placebo-controlled study. Eur Urol. 2007;52:1768-74.

Mosah H, Khazaal F, Sabih H. Effect of L-carnitine and raspberry ketones on metabolic parameters in Iraqi obese females, a comparative study. Int J Pharm Sci Rev Res. 2015;31:63-8.

Murthy VL, Abbasi SA, Siddique J, Colangelo LA, Reis J, Venkatesh BA, et al. Transitions in metabolic risk and long-term cardiovascular health: coronary artery risk development in young adults (CARDIA) Study. J Am Heart Assoc. 2016;5:e003934.

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;2:420-36.

Rafraf M, Karimi M, Rashidi MR, Jafari A. Effect of L-carnitine supplementation in comparison with moderate aerobic training on insulin resistance and anthropometric indices in obese women. J Zanjan Univ Med Sci Health Services. 2012;20(83).
Rahbar A, 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: 592-6.

Rondanelli M, Opizzi A, Perna S, Faliva M, Solerte SB, Fioravanti M, et al. Improvement in insulin resistance and favourable changes in plasma inflammatory adipokines after weight loss associated with two months’ consumption of a combination of bioactive food ingredients in overweight subjects. Endocrine. 2013;44:391-401.

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;84:851-7.

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: 231-7.

Shirali S, Hosseini SA, Ashtary-Larky D, Daneghian M, Mirlohi M-S. Effect of caffeine co-ingested with carnitine on weight, body-fat percent, serum leptin and lipid profile changes in male teen soccer players: A randomized clinical trial. Int J Pediatr. 2016;4: 3685-98.

Soare A, Weiss EP, Holloszy JO, Fontana L. Multiple dietary supplements do not affect metabolic and cardiovascular health. Aging (Albany NY). 2014;6:149-57.

Steiber A, Kerner J, Hoppel CL. Carnitine: a nutritional, biosynthetic, and functional perspective. Mol Aspects Med. 2004;25:455-73.

Suzuki Y, Narita M, Yamazaki N. Effects of L-carnitine on arrhythmias during hemodialysis. Jpn Heart J. 1982;23:349-59.

Tabák AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimäki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. Lancet. 2009;373:2215-21.

Takenaka T, Kanno Y, Ohno Y, Suzuki H. Key role of insulin resistance in vascular injury among hemodialysis patients. Metabolism. 2007;56:153-9.

Wall BT, Stephens FB, Constantin-Teodosiu D, Marimuthu K, Macdonald IA, Greenhaff PL. Chronic oral ingestion of L-carnitine and carbohydrate increases muscle carnitine content and alters muscle fuel metabolism during exercise in humans. J Physiol. 2011;589:963-73.

Xia Q, Chen Z-X, Wang Y-C, Ma Y-S, Zhang F, Che W, et al. Association between the melatonin receptor 1B gene polymorphism on the risk of type 2 diabetes, impaired glucose regulation: a meta-analysis. PLoS One. 2012;7:e50107.

Xu Y, Jiang W, Chen G, Zhu W, Ding W, Ge Z, et al. L-carnitine treatment of insulin resistance: A systematic review and meta-analysis. Adv Clin Exp Med. 2017;26:333-8.

Yonei Y, Takahashi Y, Watanabe M, Yoshioka T. A double-blind, randomized controlled trial (RCT) of L-carnitine and conjugated linoleic acid-based health food with health claims. Anti-Aging Med. 2007;4:19-27.

Yonei Y, Takahashi Y, Hibino S, Watanabe M, Yoshioka T. Effects on the human body of a dietary supplement containing L-carnitine and garcinia cambogia extract: a study using double-blind tests. J Clin Biochem Nutr. 2008;42:89-103.

Zhang J-j, Wu Z-b, Cai Y-j, Ke B, Huang Y-j, Qiu C-p, et al. L-carnitine ameliorated fasting-induced fatigue, hunger, and metabolic abnormalities in patients with metabolic syndrome: a randomized controlled study. Nutr J. 2014;13:110.