The effects of L-carnitine supplementation on glycemic control: a systematic review and meta-analysis of randomized controlled trials

Fathizadeh, Hadis; Milajerdi, Alireza; Reiner, Željko; Kolahdooz, Fariba; Asemi, Zatollah

EXCLI Journal 2019;18:631-643 – ISSN 1611-2156
Received: May 16, 2019, accepted: August 03, 2019, published: August 19, 2019

Original article:

THE EFFECTS OF L-CARNITINE SUPPLEMENTATION ON GLYCEMIC CONTROL: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Hadis Fathizadeh[1], Alireza Milajerdi[2], Željko Reiner[3], Fariba Kolahdooz[4], Zatollah Asemi[*5]

[1] Department of Microbiology, Kashan University of Medical Sciences, Kashan, Iran
[2] Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran; Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
[3] Department of Internal Medicine, University Hospital Centre Zagreb, School of Medicine, University of Zagreb, Zagreb, Croatia
[4] Indigenous and Global Health Research, Department of Medicine, University of Alberta, Edmonton, Canada
[5] Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran

* Corresponding author: Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran. Tel: +98-31-55463378; Fax: +98-31-55463377. E-mail address: asemi_r@yahoo.com (Z.Asemi)

http://dx.doi.org/10.17179/excli2019-1447

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

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

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

EXCLI Journal 2019;18:631-643 – ISSN 1611-2156
Received: May 16, 2019, accepted: August 03, 2019, published: August 19, 2019

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*

EXCLI Journal 2019;18:631-643 – ISSN 1611-2156
Received: May 16, 2019, accepted: August 03, 2019, published: August 19, 2019

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 (Stata Corp., 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.

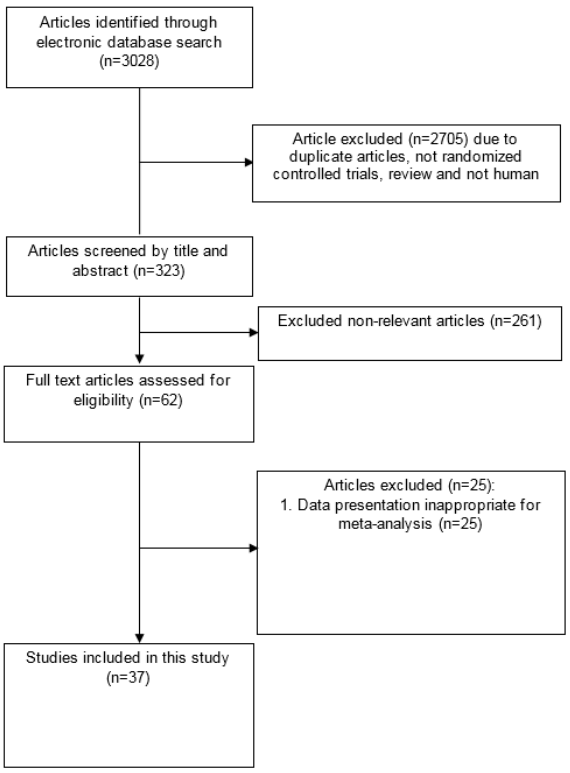

Figure 1: Literature search and review flowchart for selection of studies

EXCLI Journal 2019;18:631-643 – ISSN 1611-2156
Received: May 16, 2019, accepted: August 03, 2019, published: August 19, 2019

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
Gonzalez-Ortiz et al.	2008	Mexico	6/6	4 weeks	30-60	3000 mg L-carnitine
Yonei et al.	2008	Japan	17/18	8 weeks	48.3±6.9	600 mg L-carnitine + 500 mg Garcinia cambogia extract
Malaguarnera et al.	2009	Italy	40/41	12 weeks	49±13, 48±11	2000 mg L-Carnitine
Galvano et al.	2009	Italy	37/38	16 weeks	30-70	2000 mg L-carnitine + 20 mg simvastatin
Malaguarnera et al.	2009	Italy	40/40	12 weeks	40-70	2000 mg L-carnitine + 20 mg simvastatine
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	USA	10/4	8 weeks	18-44	1000 mg Glycine propionyl-L-carnitine
Bloomer et al.	2009	USA	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	Italy	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
Rafraf et al.	2012	Iran	11/11	8 weeks	34.4±5.48, 36.5±7.33	2000 mg L-carnitine
Rafraf et al.	2012	Iran	11/11	8 weeks	34.8±6.25, 36.1±7.2	2000 mg L-carnitine + exercise
Hlais 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

EXCLI Journal 2019;18:631-643 – ISSN 1611-2156
Received: May 16, 2019, accepted: August 03, 2019, published: August 19, 2019

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

EXCLI Journal 2019;18:631-643 – ISSN 1611-2156
Received: May 16, 2019, accepted: August 03, 2019, published: August 19, 2019

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	
				I^2 (%)	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

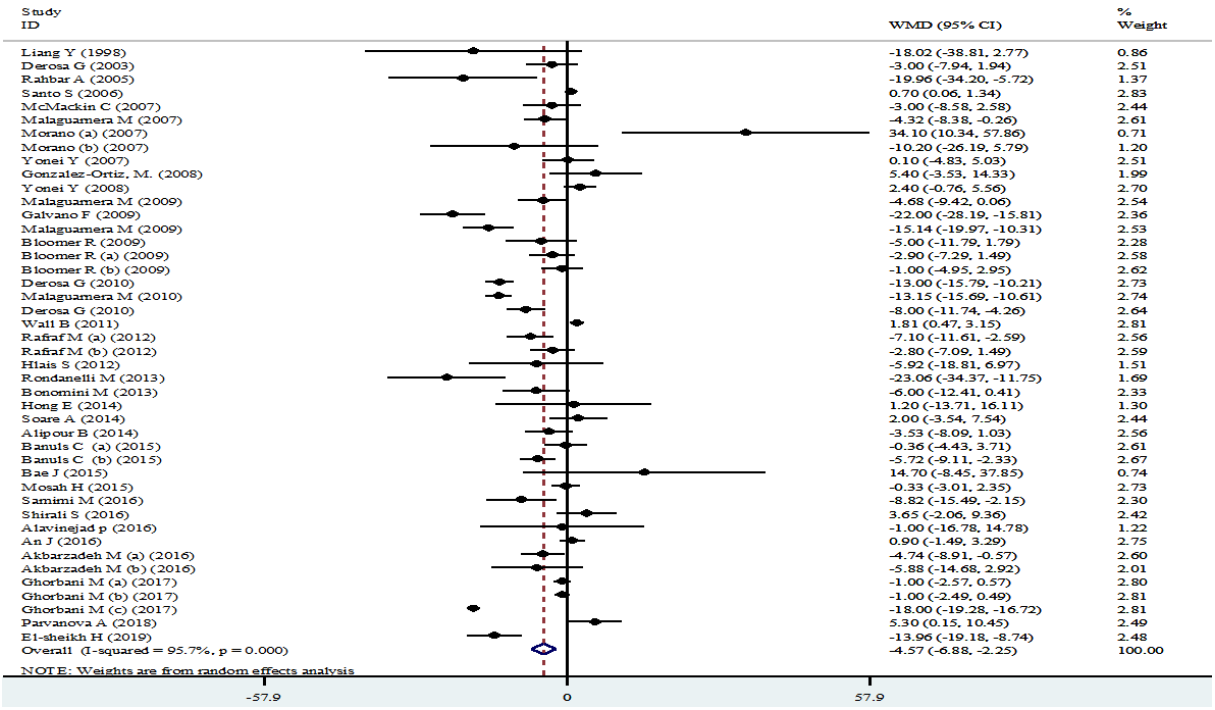

Figure 2A: FPG

EXCLI Journal 2019;18:631-643 – ISSN 1611-2156
Received: May 16, 2019, accepted: August 03, 2019, published: August 19, 2019

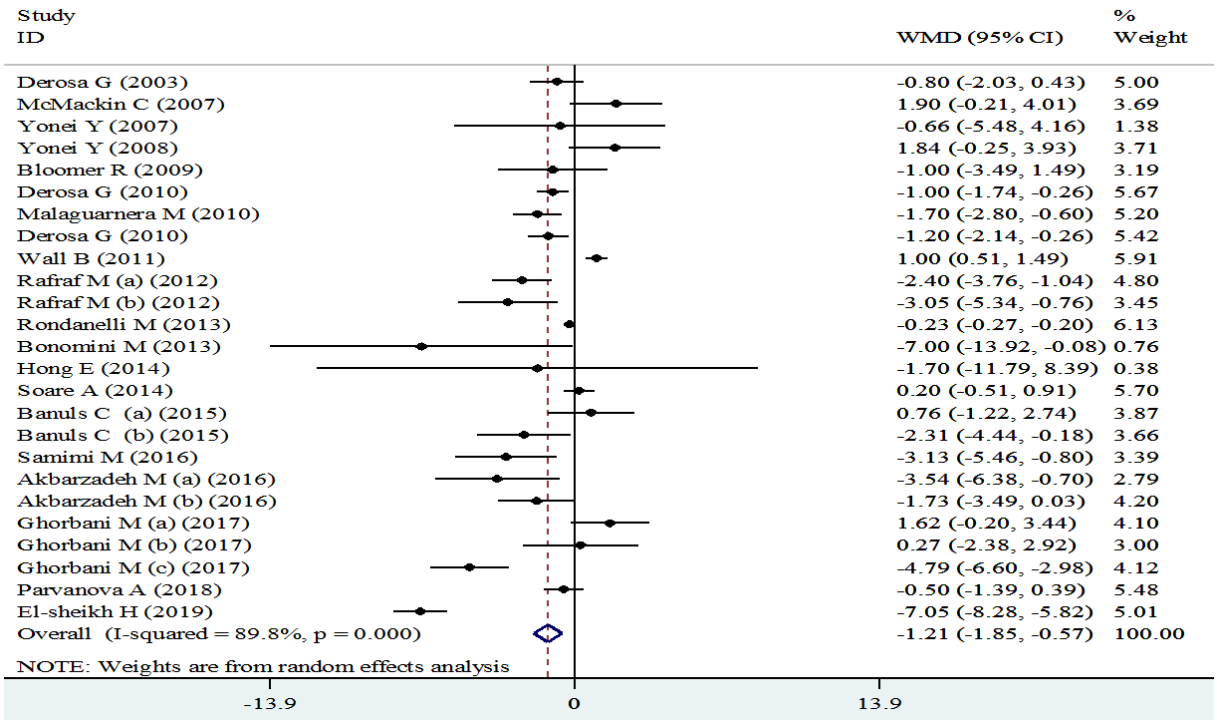

Figure 2B: **Insulin**

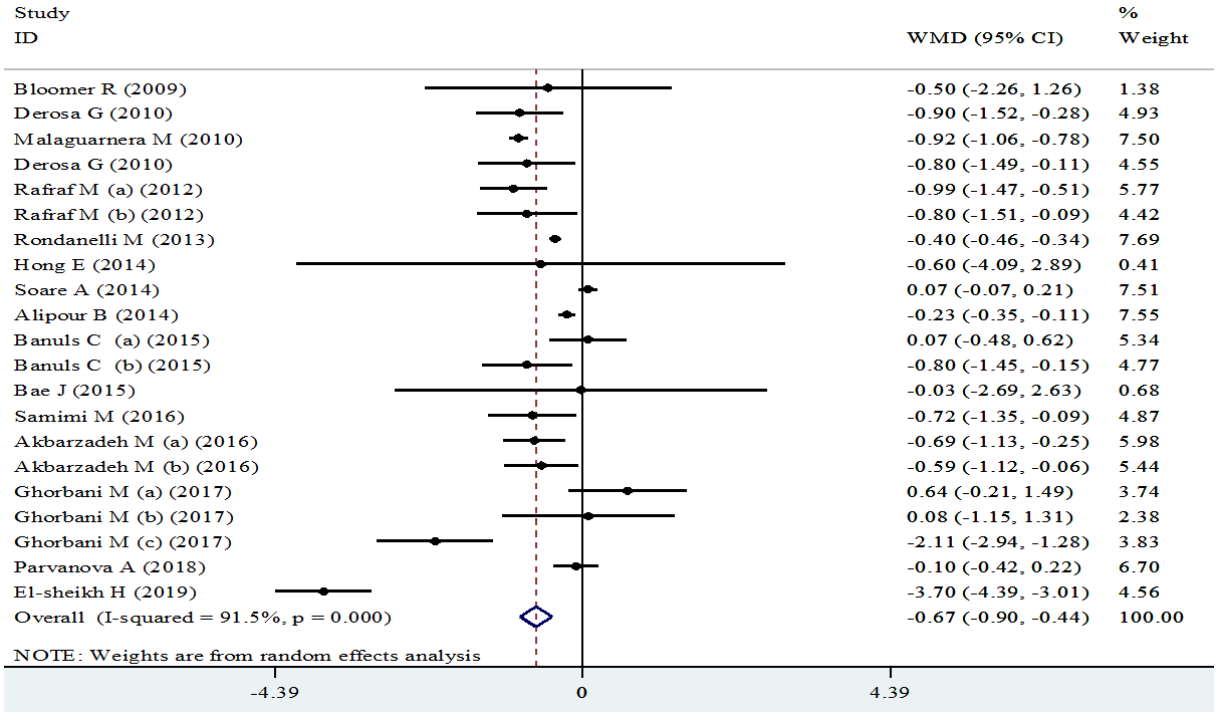

Figure 2C: **HOMA-IR**

EXCLI Journal 2019;18:631-643 – ISSN 1611-2156
Received: May 16, 2019, accepted: August 03, 2019, published: August 19, 2019

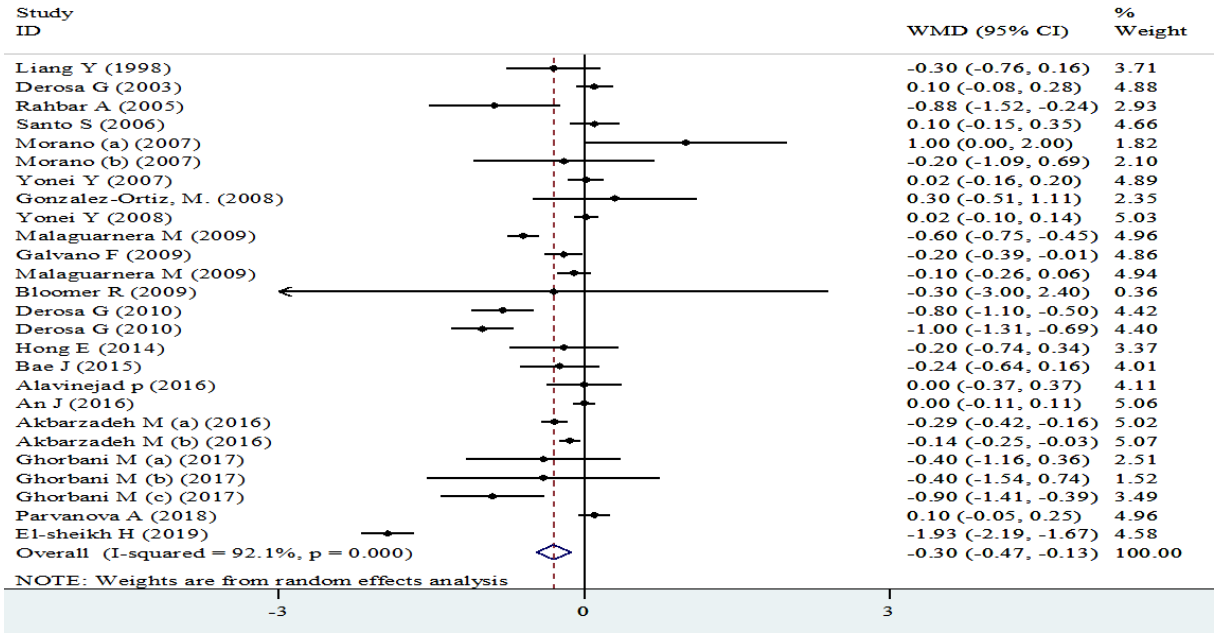

Figure 2D: **HbA1c**

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	I^2 (%)
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	00.0
		≥2000 mg/day	28	-1.26	-1.75, -0.77	92.8
	Study duration	<3 month	17	-6.37	-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	00.0
		Liver disease	2	-12.74	-15.25, -10.24	71.1
		Other diseases	1	0.90	-1.49, 3.29	-

EXCLI Journal 2019;18:631-643 – ISSN 1611-2156
Received: May 16, 2019, accepted: August 03, 2019, published: August 19, 2019

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	00.0
	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	00.0
	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	00.0
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	00.0
		Liver disease	2	-0.92	-1.06, -0.78	00.0
	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	00.0
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	65.1
		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

EXCLI Journal 2019;18:631-643 – ISSN 1611-2156
Received: May 16, 2019, accepted: August 03, 2019, published: August 19, 2019

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.

Acknowledgements

Not applicable.

Funding

Not applicable.

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, Safaeian 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 SH, 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 fibre and l-carnitine improves glucose homoeostasis 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). 2009a;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.

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;25:1429-39.

Derosa 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.

Derosa 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.

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. 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 apoprotein (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, Martínez-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, 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;34:1674-82.

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. J Gastroenterol Hepatol. 2014;29:1449-57.

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, 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; 86:1738-44.

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. 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 obesewomen. 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, Yoshoka 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.