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Original article

Effect of L-Carnitine Supplementation during Exercises on Blood Fatigue and Energy Metabolism Factors: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract. *Background and aim:* Probably L-Carnitine can induce the reduction of lactate production and improvements of performance due to the long chain fatty acid oxidation reinforcement. According to this, the aim of this review was to assess the effects of L-Carnitine consumption on blood lactate and glucose. *Methods:* Scopus, Medline and Google scholar systematically searched up to April 2021. The Cochrane Collaboration tool used for the quality of studies. Random effects model, weighted mean difference (WMD) and 95% confidence interval (CI) applied for the overall effect estimating. The heterogeneity between studies evaluated applying the chi-squared and I^2 statistic. *Results:* The outcomes showed a significant effect of L-Carnitine supplementation on reducing lactate (weighted mean difference [WMD] = -0.65 mmol/L; 95% CI: -0.86, -0.43; P <0.001)). In addition, a subgroup analysis indicated a significant reduction in lactate concentrations, according to some of follow-ups post exercise, all dose of L-Carnitine and duration of studies, both aerobic and anaerobic exercise type, both trained and untrained participant and trials using L-Carnitine supplementation type. *Conclusions:* These results showed that L-Carnitine supplementation can reduce fatigue and improve performance of aerobic and anaerobic exercise.

Key words: L-Carnitine, lactate, fatigue, glucose, energy metabolites, meta-analysis

Introduction

Exercise is known to release several hormones related to energy production, metabolism, and changes in the concentrations of anabolic and catabolic hormones due to the physiological stress caused by exercise. Following chronic training, the hormonal response to exercise potentiates gains in muscle strength (1). Exercise damages certain muscle fibers that must later undergo a repair process. Hormones, dietary nutrients, and growth factors interact to regulate this restoring of skeletal muscle proteins (2). As a result, dietary energy and nutrients may influence hormonal concentrations independently of exercise and thus help to mediate physiological mechanisms related to recovery from exercise. Besides, exercise can cause fatigue due to adenosine triphosphate (ATP) depletion and excessive production of fatigue substances such as ammonia and lactate (3). Finally, the accumulation of fatigue factors can lead to poor performance (4). Generally, the grade of fatigue depends on internal factors (such as energy storage, muscle mass, and muscle fiber type), while external factors (such as exercise intensity and exercising period) and decline in muscle contraction are closely

related to the stimulation of fatigue-triggering metabolites, such as lactate (5).

L-Carnitine (L-3-hydroxytrimethylaminobutanoate) is a natural compound that biosynthesize in mammals' liver and kidneys from methionine and lysine essential amino acids requiring vitamin B6, vitamin C, niacin and catalysis reaction enzymes or intake through food (6-8). Carnitine dietary sources are dairy products and red meat; however, produced supplements are accessible and also have been shown to be safe in humans (9). L-Carnitine supplementation has gained popularity many years because of its ability to improve performance. Carnitine is stored in skeletal muscle, as well as in much lower concentrations is found in plasma (10). Two distinct mechanisms have been proposed for potential advantages of applying L-Carnitine to enhance performance. L-Carnitine is necessary for the long-chain fatty acids (carbon chain length = 10) transport across the inner- and outer-mitochondrial membranes (carnitine palmitoyltransferanse I and II, respectively) (11). Another feasible L-Carnitine function is the acetyl CoA/CoA ratio maintenance, which would reduce the pyruvate dehydrogenase complex inhibition and increase the pyruvate to acetyl CoA conversion (6). Therefore, accumulation of lactate could be decreased during exercise and result in increased plasma glucose, maximal and peak power, VO2max and enhanced performance (12).

L-Carnitine might therefore be more important in supporting the immediate recovery period after exercise. However, previous study results have often been contradictory as to the effect of L-Carnitine on blood fatigue and energy metabolism factors after exercise. The purpose of the present systematic review and meta-analysis is, hence, to examine studies that assessed blood fatigue and energy metabolism factors to intake of L-Carnitine supplementation after exercise.

Methods

Strategy of Search

Current review study was presented according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (13). A computerized search was carried out from inception to April 2021 applying diverse databases including Scopus, PubMed, ISI Web of Science and a supplementary search in Google Scholar. The literature search was restricted to English articles. The following MeSH and non-MeSH terms and their combinations were used, including: "carnitine", "L-carnitine", "levocarnitine", "acetyl carnitine", "ACAL", "exercise", "physical exercise", "eccentric exercise", "aerobic exercise", "athlete", "fatigue", "fatigue substance" "lactate", "energy metabolites", "glucose", "energy metabolites", "controlled trial", "randomized", "randomised", "random", "randomly", "randomized clinical trial", "RCT", "blinded", "double blind", "double blinded", "trial", "controlled clinical trial", "crossover procedure", "crossover trial", "double blind procedure "and "equivalence trial". Reference lists of all articles were screened for more eligible articles.

Criteria for Eligibility

Articles were elected according to the Population-Intervention-Comparator-Outcomes-Study design (PICOS) (13), including: The Population (healthy participants aged more than eighteen years old without muscles damage or injury history), Intervention (L-Carnitine supplementation), Comparison (matched control group), Outcome (blood fatigue and energy metabolism indices including lactate and glucose), that were performed in study design of randomized controlled trials (RCTs).

All RCTs were included in the current meta-analysis if met our inclusion criteria: 1) original researches in RCT study design; 2) participants received oral L-Carnitine supplementation, as a nutritional strategy; 3) presented at least one of fatigue and energy metabolism indices (lactate or glucose concentration); 4) reporting interest data as mean and standard deviation (SD) of lactate or glucose in both groups. Exclusion criteria were: 1) consuming L-Carnitine mixture in supplementation group only (vitamins and etc.), not including a placebo group; 2) animal studies; 3) trials without control groups, nonrandomized or semi experimental trials; 4) case reports, editorial articles or letters to editor; 5) duplicate articles with same participant.

Strategy of Selection

Following initial search, all papers recorded in manual searches or electronic searches were entered into EndNote software for checking (EndNote X6, Thomson Reuters, New York). According to search strategy, titles and abstracts of papers were screened. Papers were assessed independently by two authors and selected based on the inclusion criteria. Papers including eligibility criteria in the title and abstract checking were selected to be evaluated by full-text. If our inclusion criteria met, all of RCTs were included in current meta-analysis. We applied a pre-design form to select papers eligible for inclusion in the review, according to the data within the full-text. Contradictions between the reviewer authors were dissolved by third researcher or consensus.

Extraction of Data

Two independent reviewers extracted interest data applying a standardized electronic form (Excel, Microsoft Office) including: first author's name, country and year of publication, design of research, sample size, age and gender of participants, duration of intervention and dose of L-Carnitine. In addition, authors extracted baseline and after the intervention mean and SD of interest data (plasma fatigue factor (lactate) and outcome measure of energy metabolism factor (glucose)). Any presented standard errors (SE) of mean, were changed to SDs via this formula: (SD = SEM × √n (n is the subjects number in intervention and placebo groups). Finally, in papers that depicted data in figures, extraction of data was carried out applying Graph Digitizer 2.24 software (14).

Quality of Studies

As regards it has been indicated that inclusion of high risk of bias RCTs may distort the results of a meta-analysis study (15, 16), the Cochrane Collaboration tool was used for measuring the risk of bias. All the included RCTs quality were assessed by these items: randomization sequence generation; allocation concealment; blinding of participants, personnel, investigator and assessor, and attrition rates. Mentioned items were given a rating of low, unclear or high risk of bias. A study was ranked low, medium, or high risk bias overall, according to the key items of participants and assessor blinding, allocation concealment and reporting of attrition rates (Low = Low risk of bias for all key items, Medium = Low or unclear risk of bias for all key items and High = High risk of bias for one or more key items) (15).

Analysis and treatment effect measures

Mean differences and SD were computed for continuous measures for every trial. Standardized mean changes were used for variables pooled on the different scales. For papers with no mean change SD, this formula were applied: SD change = square root [(SD final ^{2}+SD baseline^2) - (2 × 0.8 × SD final × SD b aseline)] (17). Heterogeneity of studies was evaluated applying the chi-squared ($\chi 2$) test and quantified by the I^2 statistic, which reports the percentage of the total variation across trials that is attributable to heterogeneity rather than to chance. P-value of <0.05 was defined as significant heterogeneity.

For estimating the overall effect, the weighted mean differences (WMDs) with 95 percent confidence intervals (CIs) was calculated using the random effects model. To evaluate whether the outcomes could have been influenced by a single study distinctly, a sensitivity analysis was carried out (18). Also, subgroup analysis was performed, according to follow-ups measurements post exercise (Immediately, < 15 minutes, ≥ 15 minutes to < 60 minutes and ≥ 60 minutes' post exercise), dose of L-Carnitine (lower than 3 g/day and 3 g/day or higher), duration of trials (acute (single dose), 3 weeks and more than 3 weeks), exercise type (aerobic and anaerobic), train status (trained and untrained) and carnitine type (L-Carnitine or L-Carnitine L-Tartrate). Furthermore, Egger's regression asymmetry and test Begg's rank correlation test used to evaluate publication bias. The effect sizes versus their corresponding SE (differences in means) depicted by funnel plots. Moreover, statistical analyses were conducted applying STATA 11.2 software (StataCorp, College Station, Texas, USA).

Results

Findings from search and included studies overview

Our search led to 215 related studies. After duplicates removing, an extensive titles and abstracts screening was conducted on 211 studies. After checking the inclusion and exclusion criteria for the eligibility, 25 papers remained. At last, 14 articles, including, 51 effect sizes for lactate concentration and 32 effect sizes for glucose (19) concentration were identified in the present meta-analysis, that investigated a total of 308 and 208 subjects respectively. The numbers are inclusive of subjects who were dropouts in some studies. All subjects tended to be young aged 20.1 – 48 years. Furthermore, all subjects were men, except in one study that both gender participated (n = 36) (20).

The selection procedure and reasons for excluding the studies presented in Figure 1 and Table 1 indicates the basic characteristics of the studies in our review.

Briefly, the papers were published between 1988 and 2018. The total subjects number who completed

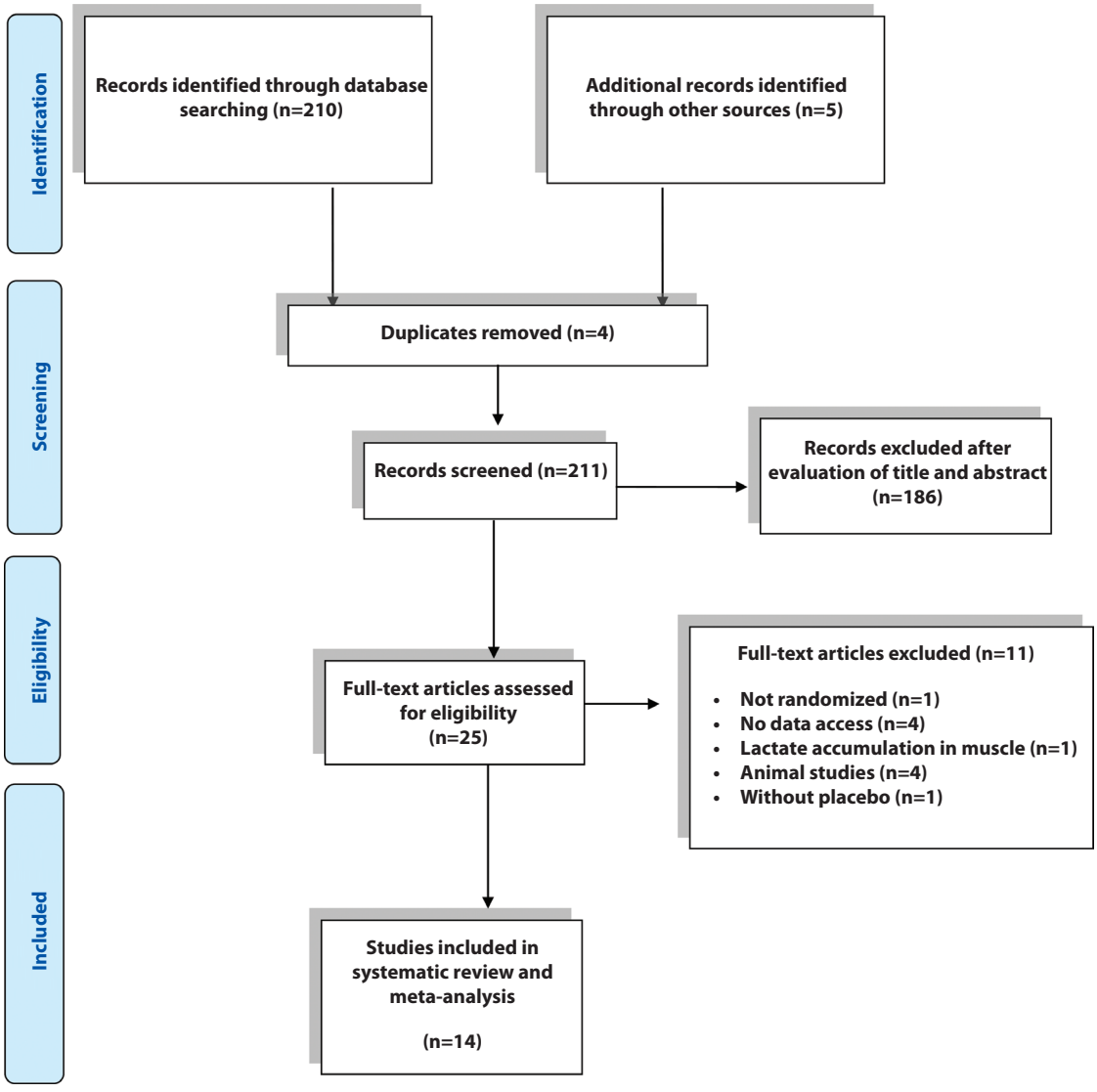

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection process.

Table 1. Characteristics of the included studies

Author (year)	Study Design Characteristics							Average age (y)	Sample Size		Exercise type	Lactate	Glucose
	design	country	training status	carnitine dose (g/d)	carnitine type	duration (d)	gender		carnitine	control			
Koozehchian et al. (2018)	RP	USA	T	2	LC	1 21 42 63	M	25	12	11	An	↓ ↓ ↓ ↓	
Arazi et al. (2017)	RP	Iran	T	3	LC	1	M	21	9	9	A An	↓ ↓	↓ ↑
Kashef et al. (2017)	CP	Iran	U	3	LC	1	M	26.4	10	10	A	↓	≡
Yu Ho et al. (2010)	CP	USA	U	2	LCLT	21	M F	48.2	9	9	An	≡ ≡	≡ ≡
Spiering et al. (2007)	CP	USA	U	2 1	LCLT	21	M	22	8	8	An	≡ ≡	≡ ≡
Kraemer et al. (2006)	CP	USA	T	2	LCLT	21	M	22	10	10	An	≡	≡
Broad et al. (2005)	CP	Scotland	T	3	LCLT	1 28	M	32	19	19	An	≡ ≡	≡ ≡
Rubin et al. (2001)	CP	USA	T	3	LCLT	21	M	23.7	10	10	A		≡
Ransone et al. (1997)	CP	USA	T	2	LC	21	M	21	25	25	A	≡	≡
Colombani et al. (1996)	CP	Switzerland	T	2	LC	1	M	36	7	7	A	≡	≡
Trappe et al. (1994)	CP	USA	T	4	LCLT	7	M	20.1	10	10	A	≡	
Vukovich et al. (1994)	CP	USA	U	7	LCLT	1	M	26.8	8	8	A	≡	≡
Siliprandi et al. (1990)	CP	Italy	T	2	LC	1	M	24	10	10	A	↓	
Oyono-Enguelle et al. (1988)	CP	France	U	2	LC	28	M	23	10	10	A	↓	≡

LC = L-Carnitine; LCLT = L-Carnitine L-Tartrate; A = Aerobic; An = Anaerobic; RP = randomized controlled trial; CP = cross-over studies; M = male; F = Female; D=Days; Y=years; T=trained; U = untrained; # Excluded from meta-analysis; ^ Unspecified or unknown

the trials in inclusion criteria was 154 subjects in the supplement and 154 in the placebo groups for lactate concentration and 108 subjects in the supplement and 100 in the placebo groups for golucose concentration. The dose of L-Carnitine supplementation was 1 to 7 g/day among these studies and the duration of them ranged between 1 day to 7 weeks. All studies used a randomized crossover design except two studies (21, 22) that used randomized and placebo-controlled, and both of them had the design of double-blind. The effect of L-Carnitine on lactate and glucose concentration together was examined in 7 studies (9, 21, 23-27); 5 studies only reported lactate concentration (20, 22, 28-30) and two studies only reported glucose concentration (9, 31).

Most of the studies measured several follow-up time for each index (e.g., blood fatigue and energy metabolism indices for intervention and placebo immediately, 3, 5, 10, 15, 20, 30, 40, 45, 50, 60, 90, 120 minutes and 24 hours after exercise). We concentrated on results presented immediately post exercise and subsequent minutes and hours (< 15 minutes, ≥ 15 minutes to < 60 minutes and ≥ 60 minutes' post exercise). Fourteen trials in 11 studies had a follow-up time immediately post exercise (9, 20, 21, 23-26, 28-30, 32); Twelve trials in 5 studies reported < 15 minutes follow-up times (22-24, 27, 32); Twenty three trials in 5 studies had ≥ 15 minutes to < 60 minutes follow-up times (20, 22-24, 27) and Seven trials in 4 studies reported follow-ups at ≥ 60 minutes post exercise (20, 24, 25, 31).

Quality assessments outcomes

The quality details of bias assessment indicated in Table 2. In brief, participant's random allocation was illustrated in all included studies. Nevertheless, two articles mentioned the random sequence generation method (22, 25). Only two articles presented allocation concealment (25, 32). All articles indicated low risk of bias according to incomplete outcome. For selective outcome reporting, most of articles had a low risk of bias; although, two studies represented unclear risk of bias based (28). Moreover, all articles had a unclear or high risk of bias for participants and personnel blinding and outcome assessors blinding except one study that indicated low risk regarding participants, personnel and outcome assessment blinding (28) and just two studies had low risk of bias regarding blinding outcome assessors (25, 30). Most articles reported low risk of bias about other potential threats to validity including a potential source of bias related to the particular study design applied; or had some problem like study has been claimed to have been fraudulent. Finally, most of studies had medium overall risk of bias, just one study had low overall risk of bias (25) and 4 studies had high overall risk of bias (23, 26, 28, 32).

Findings from the meta-analysis

L-Carnitine supplementation effects on lactate concentration

According to analysis on 51 effect sizes, in overall, L-Carnitine supplementation decrease lactate concentration significantly: (WMD = -0.65 mmol/L; 95% CI: -0.86, -0.43; P <0.001). Significant heterogeneity observed among the articles (Cochran's Q test = 261.71, P = 0.000, I^2 = 80.9%) (Fig. 2).

For assessing if the L-Carnitine supplementation effect on serum lactate concentration is different according to subgroups, meta-analysis was carried out based on follow-ups post exercise, L-Carnitine dose, studies duration, training status, carnitine type and exercise type (Tab. 3). Some of subgroup analysis showed that carnitine consumption have a significant reduction effect on lactate concentrations in trials with < 15 minutes post exercise and ≥ 15 minutes to < 60 minutes measurement of lactate after exercise, both lower and more than 3 g/day carnitine consumption, all trial duration (acute, 3 weeks and more than 3 weeks), trials on both trained and untrained participant, trials using L-Carnitine supplementation type (not L-Carnitine L-Tartrate) and both aerobic and anaerobic exercise type.

L-Carnitine supplementation effects on glucose concentration

L-Carnitine supplementation effect of the on glucose concentration was assessed in 32 effect sizes and analysis revealed a significant change in glucose concentration in pooled mean difference from inverse

Table 2. Cochrane Risk of Bias Assessment

Study	Random Sequence Generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall Risk of Bias
Koozehchian et al. (2018)	L	U	U	U	L	L	L	Medium
Arazi et al. (2017)	U	U	U	U	L	L	L	Medium
Kashef et al. (2017)*	U	H	U	U	L	L	H	High
Yu Ho et al. (2010)	U	U	U	U	L	L	L	Medium
Spiering et al. (2007)	U	H	H	U	L	L	L	High
Kraemer et al. (2006)	U	U	U	U	L	L	L	Medium
Broad et al. (2005)	U	L	U	U	L	L	L	Medium
Rubin et al. (2001)	U	U	U	U	L	L	L	Medium
Ransone et al. (1997)	U	U	H	H	L	U	L	High
Colombani et al. (1996)	L	L	L	L	L	L	L	Low
Trappe et al. (1994)	U	U	U	L	L	L	L	Medium
Vukovich et al. (1994)	U	U	U	U	L	L	L	Medium
Siliprandi et al. (1990)	U	U	U	U	L	U	L	Medium
Oyono-Enguelle et al. (1988)*	U	H	H	H	L	L	L	High

L, low risk of bias; H, high risk of bias; M, medium risk of bias; U, unclear risk of bias.

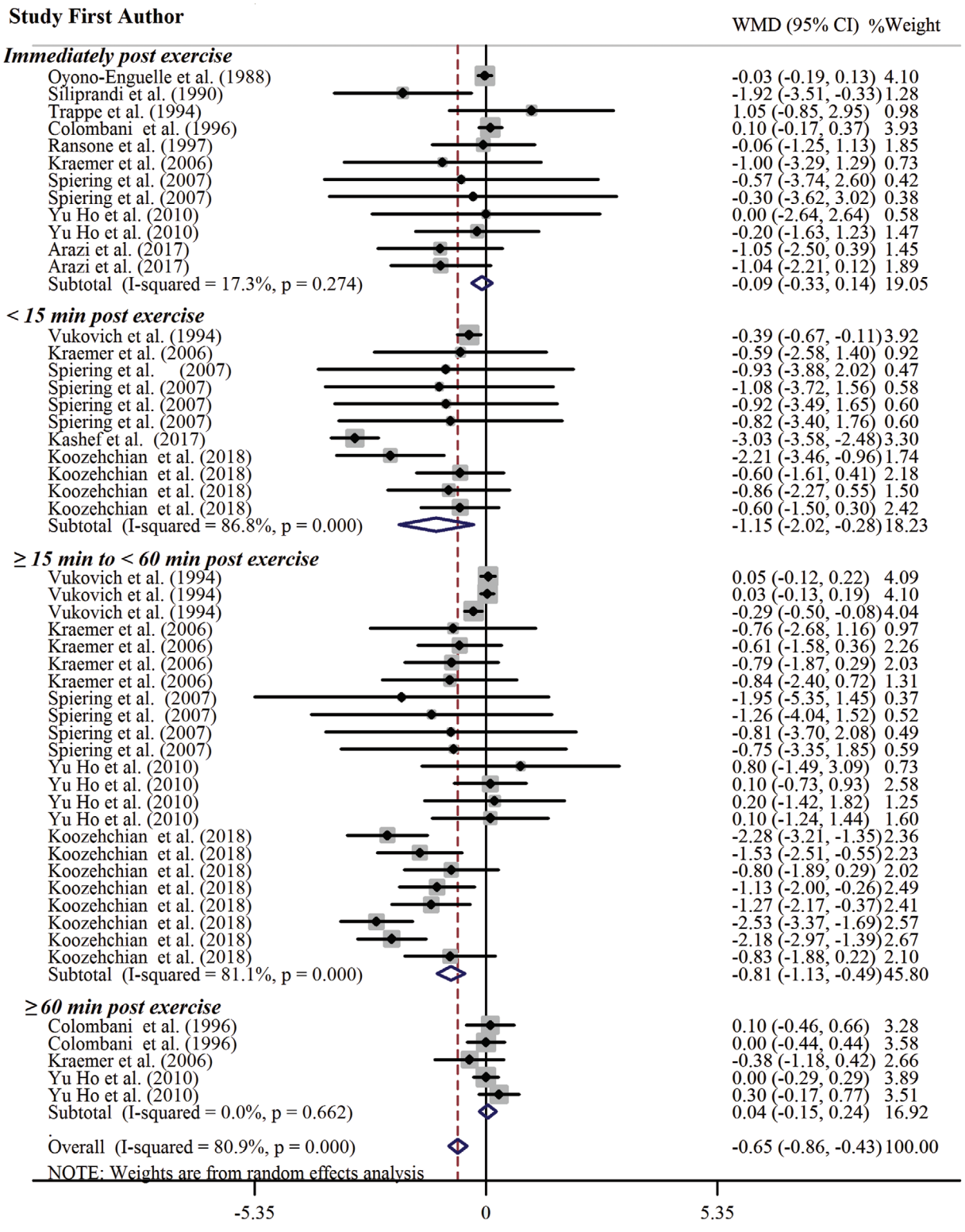

Figure 2. Forest plot of the effect of L-Carnitine supplementation on lactate concentration, WMD = weighted mean difference; CI = confidence

Table 3. Subgroup Analysis to Assess the Effect of L-Carnitine on lactate concentration.

Subgrouped by	No. of trials	Effect size[1]	95% CI		P Value	I^2 (%)
Follow-ups after exercise						
Immediately post exercise	12	-0.09	-0.32	0.14	0.431	17.3
< 15 min post exercise	11	-1.15	-2.02	-0.27	**0.010**	86.8
≥ 15 min to < 60 min post exercise	23	-0.80	-1.12	-0.48	**<0.001**	81.1
≥ 60 min post exercise	5	-0.04	-0.15	0.23	0.673	0.0
Dose of L-Carnitine						
<3 g/day	43	-0.65	-0.90	-0.40	**<0.001**	68.8
≥3 g/day	8	-0.63	-1.12	-0.14	**0.011**	94.5
Duration of supplementation						
Acute (single dose)	14	-0.56	-0.90	-0.23	**0.001**	90.8
3 weeks	29	-0.42	-0.71	-0.13	**0.004**	30.4
> 3 weeks	8	-1.26	-2.22	-0.31	**0.009**	91.0
Train status						
trained	27	-0.91	-1.27	-0.55	**<0.001**	75.9
untrained	24	-0.32	-0.61	-0.21	**0.022**	82.6
Exercise type						
Aerobic	13	-0.35	-0.66	-0.05	**0.020**	91.1
Anaerobic	38	-0.83	-1.15	-0.51	**<0.001**	63.5

[1]Calculated by random effects model.
CI = confidence interval

variance method (WMD = -0.04 mmol/L; 95% CI: -0.11, 0.04; p = 0.301). Also significant heterogeneity observed among the articles (Cochran's Q test = 17.34, P = 0.977, I^2 = 0.0%) **(Figure 3).**

To evaluate if the L-Carnitine supplementation effect on glucose concentration is different according to subgroups, meta-analysis was performed based on follow-ups post exercise, L-Carnitine dose, studies duration, training status, carnitine type and exercise type (Tab. 4). Just one of subgroup analysis revealed that carnitine supplementation resulted in a significant reduction in glucose concentration in trials applying L-Carnitine L-Tartrate (not L-Carnitine). There was no significant heterogeneity among the studies (Cochran's Q test = 16.31, P = 1.000, I^2 = 0.0%)

Publication bias and Sensitivity analysis

Any of the studies removal from the meta-analysis, create no alteration in the outcomes of the meta-analysis on serum lactate and glucose concentration based on sensitivity analysis. Funnel plots for lactate and glucose concentration were visually symmetrical **(Figure 4 & 5)**, and the results of Begg's test did not determine any evidence of publication bias in articles that evaluate the effect of L-Carnitine supplementation on lactate concentration (Begg's test, P= 0.179) and on glucose concentration (Begg's test, P = 0.926).

Discussion

To our knowledge, the efficacy of L-Carnitine has not been firmly established for fatigue and energy metabolism factors. Therefore, this systematic review and meta-analysis has sought to provide insight into the potential advantages conferred by such supplementation to enable trainers to make informed decisions as to their efficacy and usage. The results of the current

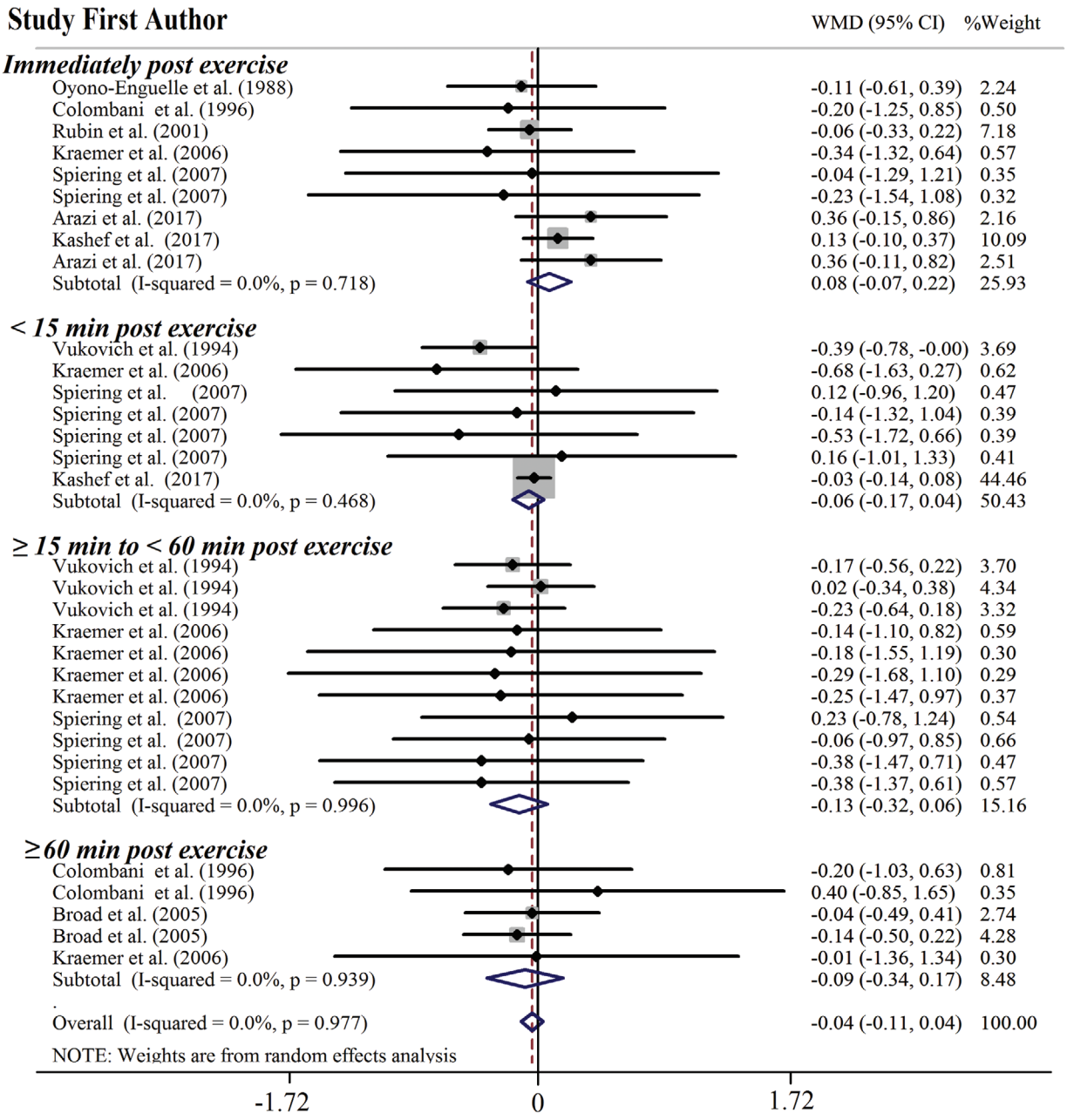

Figure 3. Forest plot of the effect of L-Carnitine supplementation on glucose concentration, WMD = weighted mean difference; CI = confidence interval.

meta-analysis, performed in 14 randomized controlled trials, revealed noticeable effects of L-Carnitine supplementation in decreasing fatigue substances levels during training protocols of different durations. The major finding of this study was the observation of significantly lower values of lactate concentration during less than 15 minutes' post exercise and between 15 minutes to 60 minutes after exercise with L-carnitine. Thus, our findings support those of previous investigators, namely, that L-Carnitine ingestion is capable of attenuating exercise-induced increases in lactate (21, 22, 26, 29, 32).

Table 4. Subgroup Analysis to Assess the Effect of L-Carnitine on Glucose concentration.

Subgrouped by	No. of trials	Effect size[1]	95% CI		P Value	I^2 (%)	p for heterogeneity
Follow-ups after exercise							
Immediately post exercise	9	0.07	-0.07	0.22	0.307	0.0	0.718
< 15 min post exercise	7	-0.06	-0.16	0.04	0.230	0.0	0.468
≥ 15 min to < 60 min post exercise	11	-0.12	-0.31	0.06	0.191	0.0	0.996
≥ 60 min post exercise	5	-0.08	-0.34	0.16	0.508	0.0	0.939
Dose of L-Carnitine							
<3 g/day	21	-0.15	-0.37	-0.06	0.154	0.0	1.000
≥3 g/day	11	-0.02	-0.12	-0.07	0.627	15.9	0.292
Duration of supplementation							
Acute (single dose)	13	-0.02	-0.11	-0.06	0.638	4.5	0.401
3 weeks and more	19	-0.12	-0.31	-0.06	0.201	0.0	1.000
Train status							
trained	15	-0.02	-0.17	0.13	0.787	0.0	0.864
untrained	17	-0.04	-0.13	0.04	0.302	0.0	0.921
Exercise type							
Aerobic	12	-0.03	-0.11	0.05	0.444	0.0	0.550
Anaerobic	20	-0.07	-0.25	0.10	0.414	0.0	0.992

[1]Calculated by random effects model.
CI = confidence interval

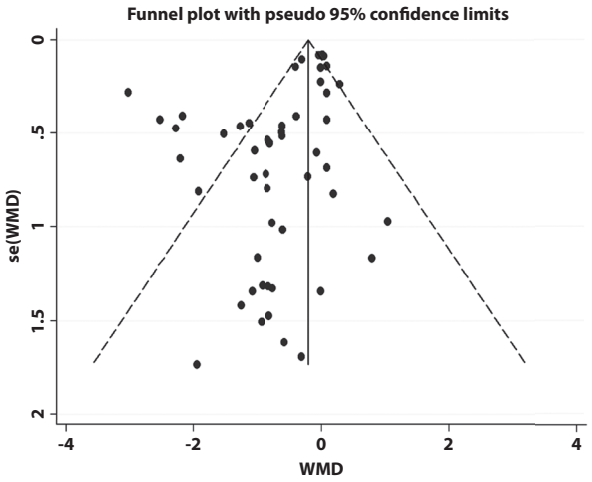

Figure 4. Funnel plot for evaluating publication bias in lactate

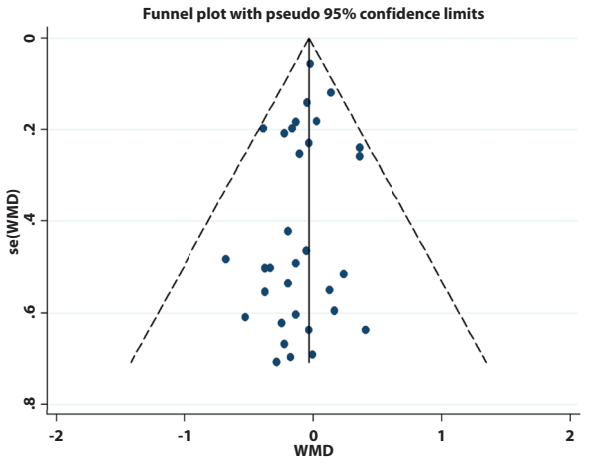

Figure 5. Funnel plot for evaluating publication bias in glucose

A review paper by Hormoznejad et al. (33) reported that, in order to assess fatigue, plasma ammonia activity and plasma lactate concentration are widely used as markers. However, the above meta-analysis was performed based on lactate. These factors are not only the most used outcomes; they are the best markers of muscle fatigue (34-36). The rate of lactate production exceeds the rate of removal during high-intensive exercise. The excess lactate facilitates acidosis and suppresses the enzymatic activation related to glycolysis, which impedes ATP synthesis and finally leads to fatigue (37).

The primary role of carnitine is on the lipids metabolism; however, evidences also support its feasible participation on the biogenesis of carbohydrates. Practically, there has been a considerable association considering the Krebs cycle and the muscle carnitine (38). Lipids oxidation process is motivated after the L-Carnitine administration (39). In the L-Carnitine supplementation field, it has been suggested that consuming this supplement can protect the cell membrane integrity, stabilizing the physiological CoA (COA) to acetyl-CoA (coA SH) ratio within the mitochondria, then leads to enhanced pyruvate dehydrogenase activity and finally decreases lactate production (40). During activities, acetyl-CoA to free CoA conversion ratio augments; therewith it leads to increased accumulation of lactate. L-Carnitine together with acetyl-CoA form acetyl L-Carnitine and stimulate fixing this ratio that leads to reduced accumulation of lactate (6). On the other hand, carbohydrate is the main substrate in activity specially in anaerobic exercise and the pyruvate converted to lactate by lactate dehydrogenase, which affects performance (41). In addition, since fat oxidation requires more oxygen compared to carbohydrate, the cardiovascular system should deliver more oxygen to muscles (42). Accordingly, L-Carnitine increases the oxygen consumption and lipids oxidation by motivating pyruvate dehydrogenase complex and pyruvate entry into the pathway of beta-oxidation (43). Also, the acyL-Carnitine production through the CoA storage buffering can be beneficial for cell function (10). High-intensity exercise is associated with increased concentrations of blood ammonia and hypoxia (44). So, the carnitine availability even in the baseline level can decrease the rate of physical function loss and inhibit muscle fatigue (45).

Furthermore, during activity, decrease or increase in blood glucose concentration is normal. Generally, light exercises do not have particular effect on blood glucose (46). If the exercise load is moderate or severe, at first blood glucose increases and if the exercise continues for a longer time, blood glucose concentration reduces and reaches lower concentration than baseline (47). However, in our study, intake of L-Carnitine for any dose and duration had no significant effect on lowering glucose concentration in the follow-up times post exercise, compared to a placebo. The increase in muscle carnitine leads to an enhance fatty acid oxidation and increase in Triacylglycerol in muscle during exercise and decreases liver glycogen breakdown that leads to lower blood glucose concentration (48). The subjects of most studies were untrained participants and considering the effect of exercise on uptake of muscle carnitine, the participants' muscles did not absorb carnitine and did not get the required effect on fat oxidation (49).

The main strength of our meta-analysis is that we considered all published clinical trials performed on the L-Carnitine supplementation effect on lactate and glucose concentration. In this field, a previous meta-analysis with 6 studies carried out by Vecchio et al. (50) had assessed the effects of L-Carnitine Supplementation on lactate levels (25, 51-55). In our Meta-analysis all relevant studies have been included, as far as the quality of available information permits, and the effects of L-Carnitine Supplementation on lactate levels have been assessed in more detail than in the previous meta-analysis. Our meta-analysis after removing 5 studies (30, 54, 56-58) because of not randomization, presenting delta change data and intervention without placebo, carried out with 13 eligible studies (19-21, 23, 25, 27-30, 32, 53, 59, 60). The difference in the numbers of included studies and participants pooled in the meta-analysis, is one of reasons for the discrepancy in results of these two meta-analysis.

Also, the main limitation in this study is considerable between-study heterogeneity for lactate concentration. Despite the high heterogeneity of the data, the meta-analysis was conducted and in our opinion, these results should not be considered reliable. Several factors can affect the high heterogeneity and the inconclusive findings that have been reported. Some of these are: There were a small number of women participants in the reviewed articles and different manufacturers of L-carnitine. In addition, the lack of controlling for baseline measures in studies because we did not access the data and different study designs should be taken into account. All these factors may contribute to the inconsistencies in results.

Conclusion

To our knowledge, this is the first systematic review and meta-analysis to evaluate the effects of L-Carnitine on fatigue and energy metabolism factors

after exercise. The current evidence-based information demonstrates that supplementation with L-Carnitine is better than passive recovery or rest after various forms of damaging and exhausting exercise. Further research is necessary to quantify L-Carnitine efficacy in a homogenous supplementation strategy and the same exercise protocol over a longer timeframe and to clarify possible interactions with diet and environment. In addition, the effects of L-Carnitine on other fatigue and energy metabolism factors, for example ammonia and free fatty acids (FFA), and the cost-effectiveness of this supplement should be clarified in further studies.

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