SYSTEMATIC REVIEW

Randomised Clinical Trial of Combined L-Carnitine Supplement and Exercise on Biochemical Markers and Exercise Performance: A Systematic Review

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ABSTRACT

Aim and design: L-carnitine supplementation combined with exercise may enhance metabolic responses and improve exercise performance. Thus, this systematic review article aims to identify the effects of the L-carnitine supplement on biochemical markers, and exercise performance when combined with exercise. **Data Sources:** The articles are screened and reviewed based on titles, abstracts and keywords. Only peer-reviewed studies written in the English language, dated January 2000 to March 2021, were considered in this review. **Review Methods:** The PRISMA method is used for this study. PubMed, EBSCOHost, SpringerLINK, and Scopus databases were used to systematically search. **Results:** From a search 731 articles, 12 articles were identified related to effect of L-carnitine intake with exercises on biochemical markers and exercise performance. Studies showed that L-carnitine supplementation can be consumed daily during aerobic or anaerobic exercises by different population including patients. Its combination could improve serum lipid profiles, antioxidant properties, markers of metabolic, oxidative stress, and inflammatory, and exercise performance. **Conclusion and Impact:** This review provides information regarding the beneficial effects of L-carnitine supplement with recommended dosages and exercise prescriptions on overall body health in human.
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INTRODUCTION

Dietary supplements are consumed to maintain good health, treat sickness, and act as ergogenic aids during exercise performance among elite athletes. Carnitine is a broad term that describes a few different compounds. L-carnitine is a more common form of carnitine, present in the body and many supplements. There are several other types of carnitine, in which D-carnitine is one of carnitine types. This inactive form may cause a carnitine deficiency in ones body by inhibiting the absorption of other and more useful forms (1). Secondly, acetyl-L-carnitine is possibly the most effective form for the brain and previous study suggested that it may benefit people with neurodegenerative diseases (2). Next, propionyl-L-carnitine is well-suited for circulatory issues, such as peripheral vascular disease and high blood pressure. It may boost production of nitric oxide, which improves blood flow (3). L-carnitine L-tartrate is commonly added to sports supplements due to its rapid absorption rate. It may aid muscle soreness and recovery in exercise (4). Therefore, L-carnitine and L-carnitine L-tartrate seem to be most effective for general use and enhancing exercise performance.

L-carnitine (3-hydroxy-4-N-trimethylaminobutyrate) is branched from essential amino acid derivatives and is one of the supplements that protects general health from various conditions such as renal disease (5), metabolic syndrome, and cardiovascular disease (6). Carnitine is mainly stored in skeletal muscle, but it is also found in plasma (7). Long-chain fatty acids are the primary source of energy during low to moderate exercise levels. The long-chain fatty acids' transport into the mitochondria of the liver, heart, and skeletal muscle is dependent on

L-carnitine (8). The roles of L-carnitine are to conserve muscle glycogen and facilitate fat oxidation during exercise. The conversion of fat to energy seems to be a factor in body weight loss, as a result, reduce lipid profiles (9-10).

L-carnitine affects lipid accumulation in skeletal muscle by promoting fatty acid influx into the mitochondria (11) and increasing the oxidation of dietary fatty acids (12). It also optimises the adenosine triphosphate (ATP) fuel substrate in skeletal muscle during exercise (13). These conditions could replace glycogen (6) and reduce the time to fatigue during exercise (14). L-carnitine supplement also provides antioxidant protection, increases nitric oxide production, and maintains circulating nitric oxide (15).

Previous studies by Johri et al. and Wall et al. found that 2000 mg of L-carnitine supplementation increased fatty acid oxidation in skeletal muscle and increased total carnitine content for 3 weeks and 24 weeks, respectively (6, 16). Besides, Rubin et al. also mentioned that L-carnitine has no adverse effects on metabolic and haematological safety variables in normally healthy men (17). Therefore, the consumption of L-carnitine is believed to be safe even at a high dosage up to 3000 mg.

Regarding on lipid profiles, a previous study by Lee et al. L-carnitine supplementation at a dose of 1000 mg per day showed significantly increased in high density lipoprotein (HDL) and a slight decrease in triglycerides levels but no other changes in other lipids in coronary artery disease patients (18). High HDL cholesterol levels indicate a healthy circulatory system because it carries lipids back to the liver for recycling and disposal, however, an excess of triglycerides in plasma is linked to cardiovascular disease (19).

Superoxide dismutase (SOD) and catalase (CAT) are enzymes involve in the detoxification of hydrogen peroxide (H2O2) (20). H2O2 is the main component of reactive oxygen species (ROS) that cause oxidative damage. High levels of malondialdehyde (MDA), the by product, could estimate the presence of oxidative stress in the human body. L-carnitine supplementation is shown to inhibit the activities and expressions of SOD and CAT induced by H2O2. Protection of the body cells from H2O2 is maximised due to its antioxidant properties (21). Similarly, regarding inflammation responses, these responses are necessary for host defence and natural tissue homeostasis, for example removal of toxic chemicals and damaged tissue (22).

Regarding exercise performance, a previous study by Hiatt reported that 2000 mg of L-carnitine supplement ingested twice daily combined with exercise among patients who have peripheral arterial disease (PAD) has increased their exercise duration (23). A study by Allard et al. also showed a decrease in cardiac dimension after consuming L-carnitine with exercise prescription (24). Both studies have revealed that L-carnitine could improve exercise performance among patients.

The efficiency of L-carnitine combined with exercise have been discussed in the previous studies. Nevertheless, to date, there have been few findings on the effects of L-carnitine intake with exercises on biochemical markers and exercise performance in general. Hence, this review aims to identify whether consuming L-carnitine combined with exercise could influence exercise performance, and relate to biochemical properties such as oxidative stress, inflammatory markers, and lipid profiles. Based on literature search, this is the first review that examines the effects of L-carnitine consumption in relation to exercise on biochemical markers and exercise performance.

METHODOLOGY

Data Sources

Related studies were retrieved from PubMed, EBSCOHost, SpringerLINK, and Scopus electronic databases. The selected studies were hand-searched using the selection criteria outlined below. Only peer-reviewed papers written in the English language, dated January 2000 to March 2021, were evaluated in this review. There were no attempts to contact the authors for further information. However, cross-referencing on similar published research was conducted.

Study selection and eligibility

The keywords used to search the database are according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (25): #L-carnitine and #exercise or #sports performance. Studies that used the L-carnitine supplement as an intervention and those that used exercise or physical activity as an end measure were examined. These studies covered controlled trials and laboratory research on humans, which included (i) placebo-controlled L-carnitine, (ii) L-carnitine with other carbohydrates (CHO), (iii) L-carnitine in conjunction with an exercise programme versus exercise alone, and (iv)cross-over research comparing L-carnitine supplementation with and without L-carnitine supplementation. Exercise performance or physical activity can be defined as aerobic performance, anaerobic performance, resistance training, or results of sports-specific performance tests.

Data extraction

The titles and abstracts of retrieved publications were evaluated using the following criteria to determine if the full-text manuscripts required further analysis. Each full-text manuscript was systematically assessed based on the following criteria: (1) study objectives; (2) study characteristics (study design, participants, age, and sample size); (3) intervention content (intervention types, length of intervention, or mode of exercise tested);

(4) targeted outcomes; and (5) main findings. Due to the nature of the systematic review, the findings from these studies were not merged, reanalysed, or modified.

Identification of the study

The preliminary search of the database has generated 731 possible articles. Additional manual searches from perusal the reference list (n =6) were included. After eliminating duplicates and full-text journals as well as only on human studies, 92 articles were evaluated against the selection criteria based on their titles, abstracts and keywords. A total of 80 articles were rejected because the researchers did not investigate the relationships between L-carnitine and exercise and did not meet the inclusion criteria. Only 12 full-text papers were selected in this systematic review after being assessed using the PEDro scale. Fig. 1 shows the PRISMA flow diagram for the study selection process.

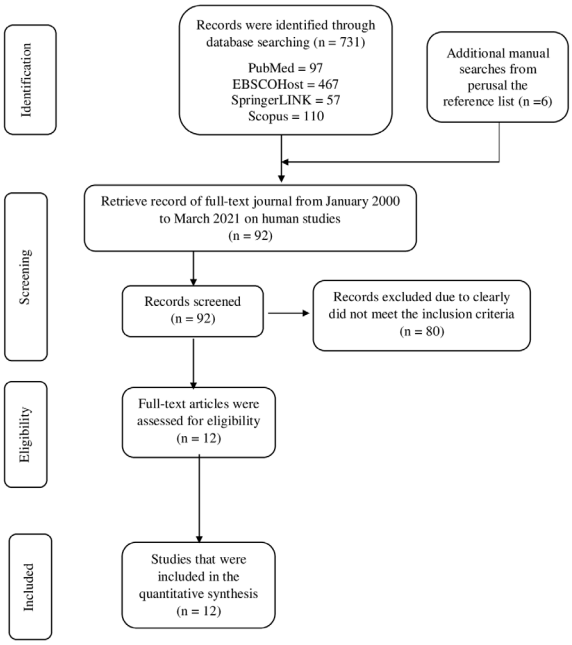

Figure 1: PRISMA flow for study selection

Quality assessment and risk of bias

The studies' methodological quality was assessed of 12 selected studies using the PEDro scale. The articles were examined by the two authors independently to reduce bias. The selected studies are high-quality, with scores ranging from 10 to 11 points and a mean score of 10.33 points. The PEDro score of selected studies are presented in Table I.

RESULTS

Search results

All 12 selected studies conducted their experimental research on humans, primarily on the effects of L-carnitine supplementation on oxidative stress and blood lactate concentration when combined with exercises such as cycling, running and squat (26-30). Five studies measured metabolic responses, cytosolic proteins, purine metabolism, and antioxidant parameters. (5, 28, 29, 32, 35). The effects of L-carnitine supplementation combined with exercise on physiological parameters, sports, and physical fitness have also been studied (5, 31-33, 36). One of these studies investigated the effects of L-carnitine supplementation on cytoplasmic Fatty Acid-Binding Proteins (FABPc) and beta hydroxyacyl-CoA dehydrogenase (β-HAD) expression. This study found that FABPc expression and β-HAD had no significant difference and remains unchanged (27). Another two of these studies reported the effects of supplementing with L-carnitine L-tartrate (LCLT) on recovery markers which decreased radical formation after physical exertion (29) and reduced muscle disruption and perceived soreness (34).

Combination of L-carnitine supplementation with exercises on biochemical markers

Table II summarises the findings of previous studies that investigated the effects of L-carnitine intake on biochemical markers and exercise efficiency. The amount of L-carnitine supplementation presented in these studies was between 1,000 mg and 4,000 mg per day of aerobic and anaerobic exercises among healthy individuals and patients' participants.

Healthy individuals were prescribed ranging from 2,000 mg to 4000 mg of L-carnitine and L-carnitine L-tartrate daily, ranging from 14 days to 7 weeks (26-30). In these studies, most of the subjects involved cycle intervention, running and squat exercises. The biochemical markers were measured on [plasma total antioxidant capacity, malondialdehyde (MDA), thiobarbituric acid-reactive substance (TBARS), creatine kinase (CK), and lactate dehydrogenase (LDH) (26)], [cytosolic fatty acid-binding protein (FABPc) expression, β-hydroxyacyl CoA dehydrogenase (β-HAD), serum carnitine concentrations, serum blood lipids, serum triacylglycerol, total cholesterol concentrations (27)], [blood metabolic; blood lactate, plasma NEFA, and plasma glycerol concentrations (28)] [purine metabolism i.e., hypoxanthine and xanthine oxidase (29)], [free radical formation (MDA), muscle tissue disruption (myoglobin, creatine kinase), and muscle soreness (30)].

In other studies who involved athletes, 2000 mg to 4000 mg L-carnitine supplement were prescribed daily combined with aerobic and anaerobic exercises (31-36). In their studies, Leelarungrayub et al. (31) measure lipid profiles including triglyceride, cholesterol, high-density lipoprotein (HDL), and very-low-density lipoprotein (VLDL). Meanwhile, blood lactate and blood glucose by Arazi and Mehrtash (32) and Broad et al. (35). Based on the previous study by Koozehchian et al. (33), blood lactate levels, oxidative stress, i.e. MDA and glutathione peroxidase (GPx) as well as total antioxidant capacity were determined. In addition, Orer and Guzell (36)

Table I: PEDro score of selected studies

Study	PEDro criterion score											Total score
	1	2	3	4	5	6	7	8	9	10	11	
Parandak et al., 2014 (26)	1	1	1	1	1	1	1	1	1	1	1	11/11
Lee et al., 2007 (27)	0	1	1	1	1	1	1	1	1	1	1	10/11
Abramowicz & Galloway, 2005 (28)	1	1	1	1	1	1	1	1	1	1	1	11/11
Ho et al., 2010 (29)	0	1	1	1	1	1	1	1	1	1	1	10/11
Burrus et al., 2018 (30)	0	1	1	1	1	1	1	1	1	1	1	10/11
Leelarungrayub et al., 2017 (31)	1	1	1	1	1	1	1	1	1	1	1	11/11
Arazi & Mehrtash, 2017 (32)	0	1	1	1	1	1	1	1	1	1	1	10/11
Koozehchian et al., 2018 (33)	1	1	1	1	1	1	1	0	1	1	1	10/11
Volek et al., 2002 (34)	0	1	1	1	1	1	1	1	1	1	1	10/11
Broad et al., 2011 (35)	0	1	1	1	1	1	1	1	1	1	1	10/11
Orer & Guzel, 2014 (36)	0	1	1	1	1	1	1	1	1	1	1	10/11
Fatouros et al., 2010 (5)	1	1	1	1	1	1	1	1	1	1	1	11/11

Table II: Effects of L-carnitine consumption and exercise on biochemical markers and exercise performance among healthy individuals and patients

Authors and year	Study population	Supplement dosage	Intervention/ exercise program	Outcome measures	Main findings	Comments
Parandak et al., 2014. (26)	Double-blind and randomised design. *n* = 21; participants were divided into L-carnitine (C) and placebo (P) groups.	2,000 mg	Intervention group performed 14 km run on the track for two weeks.	Plasma total antioxidant capacity (TAC), malondialdehyde (MDA), thiobarbituric acid-reactive substance (TBARS), creatine kinase (CK), and lactate dehydrogenase (LDH) were measured.	Total antioxidant capacity was significantly higher in the C group compared to the P group. Serum MDA-TBARS, CK, and LDH were significantly decreased in the C group compared to the P group.	Lipid peroxidation and muscle damage markers can be induced by L-carnitine supplementation and alleviate the effect.
Lee et al., 2007 (27)	Single-blind and randomised study designs. *n* = 28; Untrained, healthy males; placebo (CON), exercise training (ET), carnitine supplementation (CS), and exercise training and carnitine supplementation (CET).	4,000 mg	Intervention groups performed 40 minutes on a bicycle ergometer at 60% of maximal oxygen uptake (VO_{2max}) five times a week for six weeks.	Cytosolic fatty acid-binding protein (FABPc) expression and β-hydroxyacyl CoA dehydrogenase (β-HAD). Serum carnitine concentrations, serum blood lipids, serum triacylglycerol, and total cholesterol concentrations.	Serum triacylglycerol was increased in the ET and CET groups. Serum total cholesterol was reduced in ET and CS but not in CET. FABPc expression and β-HAD had no significant difference and remains unchanged.	Combining exercise training and L-carnitine supplementation does not increase FABPc expression and β-HAD activity in human skeletal muscle, indicating that the combined treatment has no additive effect on fat metabolism.
Abramowicz & Galloway, 2005 (28)	Double-blind, randomised, cross-over design. *n* = 12; healthy active males and females	3,000 mg	Intervention group performed 60 minutes of cycling exercise at 60% of their VO_{2max}.	Blood metabolic: blood lactate, plasma NEFA, and plasma glycerol concentrations.	No difference between trials for plasma NEFA No difference was observed between trials for males and females on blood lactate and plasma glycerol concentrations.	Chronic LCLT supplementation has increased the CHO oxidation in males during exercise, but this was not observed in females.
Ho et al., 2010 (29)	Double-blind and cross-over design. *n* = 18; active and healthy men and women	2,000 mg	An acute resistance exercise of four sets with 15 repetitions in the squat for male participants and the leg press for female participants. One-repetition maximum.	Biochemical markers of purine metabolism (i.e., hypoxanthine, xanthine oxidase), free radical formation (malondialdehyde), muscle tissue disruption (myoglobin, creatine kinase), and muscle soreness after physical exertion.	Increased purine metabolism, hypoxanthine, and xanthine oxidase. Increased myoglobin, creatine kinase, and muscle soreness-free. Decreased radical formation (malondialdehyde)	LCLT had reduced chemical damage to tissues after exercise and had optimised the processes of muscle tissue repair and remodelling.

Table II: Effects of L-carnitine consumption and exercise on biochemical markers and exercise performance among healthy individuals and patients (Continued)

Authors and year	Study population	Supplement dosage	Intervention/ exercise program	Outcome measures	Main findings	Comments
Burrus et al., 2018 (30)	Double-blind and randomised counterbalanced design of 10 males.	Three dosages; B1: 200 ml + L-carnitine, B2: 500 ml + 94 g CHO,B3: 500 ml + 94 g CHO.	Two exercise sessions consisted of 40 minutes of cycling at 65% of VO_{2peak}, followed by cycling to exhaustion at 85% of VO_{2peak}.	Blood lactate. Power output. Time to exhaustion.	Blood lactate was significantly lower after 10 minutes of cycling at 65% of VO_{2peak} with ingestion of L-carnitine compared to placebo. No differences were found in power output or time to exhaustion at 85% of VO_{2peak}.	Acute intake of L-carnitine and carbohydrates do not influence exercise parameters due to a lack of sufficient change in the content of L-carnitine in skeletal muscle. Different dosages of L-carnitine and CHO appeared to give different outcomes or findings.
Leelarungrayub et al., 2017 (31)	Thirty men, both sedentary and athletic, participated in a randomised study.	2,000 mg	The subjects were required to run on the treadmill continuously until 80% of their theoretical maximal heart rate (MHR)	Lipid profiles including triglyceride, cholesterol, high-density lipoprotein (HDL), and very-low-density lipoprotein (VLDL) were determined before and 40 minutes after the placebo or L-carnitine intake. Running time (RT) was recorded after a submaximal treadmill exercise test.	An increased in RT occurred after L-carnitine use in athletes compared to the sedentary. No changes were observed in lipid parameters, but triglyceride levels were reduced significantly in the athletes after L-carnitine consumption.	Acute L-carnitine supplementation possibly affects exercise performance and triglycerides in athletes rather than sedentary men.
Arazi & Mehrtash, 2017 (32)	Double-blind, placebo-controlled, and randomised study. *n* = 18 male artistic gymnasts in the supplementation or placebo groups.	3,000 mg	20 m shuttle run as an aerobic exercise protocol and running based anaerobic sprint test (RAST) as an anaerobic exercise protocol.	Blood lactate. Blood glucose. 20 m shuttle run (VO_{2max}) and a running-based anaerobic sprint test (RAST) for the anaerobic protocol (maximum power and mean power).	High in blood glucose, VO_{2max}, mean and maximum power among the carnitine group compared to the placebo group. There was a lower in lactate concentration in the carnitine group compared to the placebo group.	L-carnitine supplementation can decrease the production of lactic acid, increase blood glucose, and improve the aerobic and anaerobic performances of elite male artistic gymnasts.
Koozehchian et al., 2018 (33)	Double-blind and randomised design. *n* = 23; men ingested either placebo or L-carnitine for nine weeks.	2,000 mg	Nine weeks of resistance training, twice a week. For each exercise, participants performed 3-6 sets of 8-15 repetitions.	Wingate test (peak power and mean power). Bench press lifting volume. Leg press. Blood lactate levels. Oxidative stress: Total antioxidant capacity: MDA and Glutathione peroxidase (GPx).	Increased bench press lifting volume, leg press, mean power, peak power, total antioxidant capacity, and glutathione peroxidase (GPx). Decreased blood lactate levels and MDA.	2,000 mg of L-carnitine supplementation has improved muscle strength and anaerobic performance while decreasing post-exercise blood lactate and attenuating exercise-induced oxidative stress markers in resistance-trained athletes.
Volek et al., 2002 (34)	Double-blind, controlled, and cross-over design on 10 recreationally healthy, weight-trained men.	2,000 mg	The intervention group performed squat exercise that included five sets of 15–20 repetitions for three weeks.	Blood lactate. Plasma markers of purine catabolism (hypoxanthine and serum uric acid), Plasma malondialdehyde (MDA), and xanthine oxidase. Cytosolic proteins (myoglobin, fatty acid-binding protein, and creatine kinase). Muscle disruption and perceived soreness.	There was no difference in lactate responses between LCLT and placebo. Greater plasma hypoxanthine in the placebo. Plasma MDA was increased in both LCLT and placebo. Cytosolic proteins, myoglobin, fatty acid-binding protein, and creatine kinase were increased. Muscle disruption and perceived soreness were greater in placebo.	There was a favourable effect of LCLT supplementation on endothelial blood flow regulation during and after moderate-intensity squat exercise, with significantly less accumulation of purine degradation, free radical formation, tissue damage, and muscle soreness. LCLT is effective in assisting recovery from high-repetition squat exercises.
Broad et al., 2011. **(35)**	Double-blinded and randomised study on 15 endurance-trained male athletes; carnitine group (LC) and placebo (P) groups.	2,000 mg	80 minutes of continuous cycling at each of 20%, 40%, 60%, and 80% VO_{2peak} for 15 days.	Blood glucose concentration. Blood lactate. Rate of CHO oxidation. Rate of fat oxidation.	Blood glucose concentration was significantly lower during exercise in the LC compared to the P group at 40% and 60% workloads. Blood lactate was lower at the 80% workload, but there was no significant difference. The rate of CHO oxidation was reduced in both P and LC, while the rate of fat oxidation was higher in both P and LC.	When fatty acid availability increases, LC may induce a subtle change in substrate handling in metabolically active tissues.

Table II: Effects of L-carnitine consumption and exercise on biochemical markers and exercise performance among healthy individuals and patients (Continued)

Authors and year	Study population	Supplement dosage	Intervention/ exercise program	Outcome measures	Main findings	Comments
Orer & Guzel, 2014 (36)	Double-blind, repeated measure, and random method on 26 professional footballers.	1st dosage: 3,000 mg. 2nd dosage: 4,000 mg.	The intervention group performed running exercises at a speed of 8 $km.h^{-1}$ and then continued at 10 $km.h^{-1}$. The speed was increased by 1 $km.h^{-1}$ every three minutes until exhaustion.	Specific lactate concentrations and lactic acid. Running speeds.	Increased running speeds and deceased lactic acid and heart rate responses.	3,000 mg or 4,000 mg of L-carnitine that was taken before physical exercise prolonged the time to exhaustion. There is no correlation with different dosage of L-carnitine was measured in this study. Future study is required.
Fatouros et al., 2010. (5)	Randomised cross-over design, *n* = 12; patients. 8-week intervention: L-carnitine or placebo groups.	1,500 mg	Cardiopulmonary exercise testing was performed using cycle ergometer. An initial workload is 10–20 Watts for 1 minute. Then, the workload was increased by 5–10 Watts each minute until exhaustion.	Oxidative stress responses; Malondialdehyde (MDA), protein carbonyls (PC), catalase, glutathione peroxidase, and total antioxidant capacity (TAC). Lactate.	Increased time to fatigue, glutathione, glutathione peroxidase activity, and protein carbonyl. Decreased post-exercise lactate and MDA.	Eight weeks of L-carnitine supplementation may be effective in attenuating oxidative stress responses, enhancing antioxidant status, and improving the performance of patients with end-stage renal disease.

measured specific lactate concentrations and lactic acid in their study as the football athletes performed running exercises until exhaustion.

Fatouros et al. (5) investigated the study on 1500 mg of L-carnitine supplement with cardiopulmonary exercise testing on patients with renal disease. They measured oxidative stress responses such as MDA and protein carbonyls (PC), catalase, glutathione peroxidase, and total antioxidant capacity (TAC) as well as blood lactate.

Combination of L-carnitine supplementation with exercises on exercise performance

Table II summarises the findings of previous studies that investigated the effects of L-carnitine intake on exercise performance with exercise intervention. Four studies were involved athlete subjects and one study was involved patients have investigated the effects of L-carnitine intake combined with exercise on exercise performance on. Firstly, Leelarungrayub et al. (31) measured 2000 mg of L-carnitine with exercise that involved run on the treadmill continuously until 80% of their theoretical maximal heart rate. They measured running time (RT) was recorded after a submaximal treadmill exercise test. In addition, Arazi and Mehrtash (32) measured maximum power and mean power of running-based anaerobic sprint test (RAST) and Koozehchian et al. (33) peak power and mean power from Wingate test, meanwhile bench press lifting volume and leg press from of resistance training, twice a week. Running speed and time to exhaustion were measured by Orer and Guzell (36) by running exercises on treadmill. In renal disease patients, Fatouros et al. (5) determined the time to fatigue from cardiopulmonary exercise testing.

Effects of combined L-carnitine supplementation with exercises on biochemical markers

Table II summarises the studies on the effects of the L-carnitine supplement on humans. Regarding the oxidative stress parameters, Parandak et al. found that consuming 2,000 mg of L-carnitine supplementation daily for two weeks after running 14 km on the track could reduce all oxidative stress markers and total antioxidant capacity could increase significantly 14 days after L-carnitine supplementation and 24 hours after exercise in the L-carnitine group compared to placebo in active healthy young men (26). Meanwhile, Lee et al. (27) reported an increased in serum triacylglycerol and a reduction in serum total cholesterol levels after a 40-minute cycle at 60% of maximal oxygen uptake for six weeks when combined with 4000 mg of L-carnitine supplement among untrained healthy males. Abramowicz and Galloway also found that combination of 3000 mg with exercise performed at 60 minutes of cycling exercise of 60% of their VO2max had no difference was observed between trials for males and females on blood lactate and plasma glycerol concentrations (28). Ho et al. (29) also reported positive findings with significantly attenuation of free radical formation of MDA among middle-aged men and women with 2000 mg L-carnitine prescriptions combined with squat and leg press exercises after 3 weeks and 3 days of recovery.

There were few studies in this review article involved athletic subjects. Burrus et al. (30) reported that participants who cycled for 40 minutes at 65% of VO2peak had significantly lower blood lactate concentrations after taking the 2000 mg L-carnitine supplement compared to the placebo group after 7 weeks. In Leelarungrayub et al. (31) study, 2,000 mg of L-carnitine supplementation with exercised run on the treadmill continuously until 80% of their theoretical maximal heart rate showed a reduction in triglyceride levels in athletic compared to sedentary men. In a recent study by Arazi and Mehetash (32), they prescribed a daily dosage of 3,000 mg of L-carnitine supplement to elite male artistic gymnasts that had decrease the production of lactic acid and increase blood glucose after 20 m shuttle run as an aerobic exercise protocol and running based anaerobic sprint test (RAST) as an anaerobic exercise protocol. In combination with exercise, Koozehchian et al. prescribed resistance training for nine weeks combined with 2,000 mg of L-carnitine supplement daily and found a reduction in blood lactate and serum MDA levels in resistance-trained athletes (33). Other studies by Volek et al. (34) reported a decline in plasma MDA and increase in muscular disruption and perceived soreness after exercise among prescribed recreational weight-trained men with squat exercise after consuming 2,000 mg of L-carnitine L-tartrate daily for three weeks. Regarding 80 minutes of continuous cycling at each of 20%, 40%, 60%, and 80% VO2peak for 15 days with 2000 mg of L-carnitine supplement could lower the blood glucose at 40% and 60% workloads and blood lactate was lower at the 80% workload in endurance-trained male athletes (35). Based on the finding by Orer and Guzel (36), it was found that deceased in lactic acid and heart rate responses after running exercises until exhaustion with comparison of 3000 mg and 4000 mg L-carnitine supplementation in professional footballers.

Regarding the participant with disease, Fatouros et al. (5) found that ingesting 1,500 mg of L-carnitine supplement daily alone for post-test of plasma MDA among renal disease patients resulted in a decrease in plasma MDA compared to placebo.

Effects of L-carnitine consumptions combined with exercise on exercise physiological markers and exercise performance

Table II summarises the effects of L-carnitine intake on exercise performance. Leelarungrayub et al. (31) mentioned that the athletic men showed an increase in running time. In elite male artistic gymnasts, acute L-carnitine intake of 3,000 mg daily improves aerobic and anaerobic performance which are high in VO2max, mean and maximum power among the carnitine group compared to the placebo group (32). There were increments in bench press lifting volume, leg press volume, mean power, and peak power among resistance-trained males. Meanwhile, Orer and Guzel (36) reported that 3,000 mg and 4,000 mg of L-carnitine prolonged the time to exhaustion of the participants. In addition, a previous study by Fatouros et al. (5) also reported an increased time to fatigue on an upright stationary cycle ergometer until exhaustion in renal disease patients.

DISCUSSION

This review aims to summarise the current research to discover the impact of prescribed exercise training and L-carnitine supplementation on biochemical markers and exercise performance among healthy individuals, patients, and athletic groups. Based on current evidence, L-carnitine supplementation combined with any prescribed exercise is beneficial for overall physical characteristics, metabolic markers, and exercise performance. In this review, the types and intensities of exercises, the duration of the intervention, the dosage of supplementation that may influence the results, and the expected outcomes were taken into consideration.

Chemically, dietary carnitine is absorbed in the small intestine before entering the blood circulation (37). Rebouche et al. (38) stated that carnitine is involved in lipid metabolism inside the cells and enables the transfer of fatty acids from the cytoplasm to mitochondria for the β-oxidation process. Carnitine transportation takes place in three steps. Fig. 2 shows a schematic diagram of the metabolic roles of carnitine in skeletal muscle as adapted from Stephens et al. (39).

First, being catalysed by carnitine palmitoyltransferase 1 (CPT1), the transmembrane transport is facilitated by acylcarnitine transferase. Next, free carnitine is regenerated in the mitochondrion by the action of carnitine palmitoyltransferase 2 (CPT2). Lastly, the release of fatty acyl-CoAs enters the β-oxidation pathway inside the matrix. The system is known as the carnitine cycle. Considering free CoA is involved in the pyruvate dehydrogenase reaction and the β-oxidation

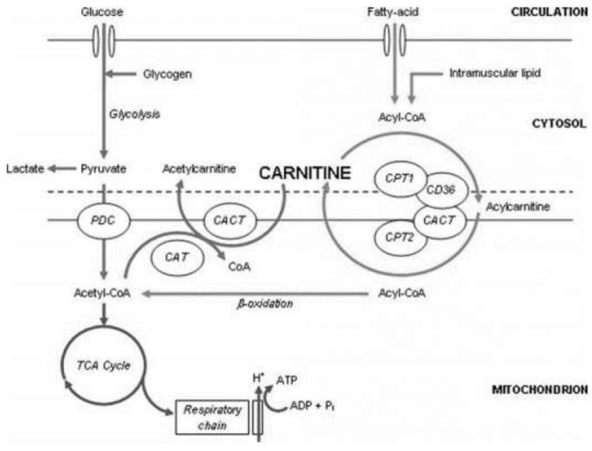

Figure 2: A schematic diagram of the metabolic roles of carnitine in skeletal muscle

process, L-carnitine contributes to the coordinated integration of fat and carbohydrate metabolism. The function of L-carnitine is crucial for β-oxidation, which is responsible for the long-chain fatty acid process in the mitochondrial cells (39), as well as moving waste products such as poorly metabolisable acyl groups from the mitochondria to the cytoplasm (11) (Fig. 2). Acetyl groups can be translocated from acyl-CoA within the mitochondrial matrix to the cytoplasm during glucose oxidation. Fatty acid oxidation could occur considering that skeletal muscle predominantly expresses an isoform of CPT1 with a low affinity for L-carnitine (11). CPT1 activity is important in weight management because it is one of the main steps in β-oxidation (7).

L-carnitine and exercises on metabolic markers and oxidative stress responses

Three studies have shown that acute consumption of L-carnitine has decreased serum lipid profiles and blood glucose levels in the blood (31, 34, 40). Leelarungrayub et al. (31) prescribed 2,000 mg of L-carnitine supplementation and showed a reduction in triglyceride levels among athletic men. However, triglyceride levels remained unchanged in inactive individuals because they had more oxidation. Therefore, high capacity to oxidise fat or triglycerides is related to endurance capacity and exercise performance in athletic rather than inactive individuals (41).

In a previous study among elite male artistic gymnast athletes by Arazi and Mehetash, consuming 3,000 mg daily of L-carnitine supplementation alone showed an increase in blood glucose levels after the aerobic and anaerobic tests (32). It is likely due to glycogen sparing and glucose storage during exercise, which leads to blood glucose accumulation. It is speculated that these findings reflect a shift in the substrate used from carbohydrates to lipids. Stephens et al. also stated that L-carnitine supplementation leads to increased fat oxidation, delayed time to exhaustion, and at the same time could reduce muscle glycolysis activity, which contributed to the high concentration of blood glucose (39). Overall, L-carnitine could enhance glycogen sparing in human blood.

L-carnitine supplementation can reduce the hazardous effects of hypoxic exercise and help with muscle damage recovery. Local hypoxia can lead to muscle injury and inflammation by decoupling ATP output from the Krebs cycle through energy consumption in the cells, resulting in ROS formation. Sarcolemma disorders produce hypoxanthine, MDA, and creatine kinase (42). As a result, low oxidative stress been accumulated in human cells after L-carnitine ingestion.

In the exercise prescriptions, Fatouros et al. (5) and Parandak et al. (26) investigated the effect of L-carnitine on oxidative stress. The reduction in oxidative stress following L-carnitine intake is associated with the body's antioxidant reserves. Local L-carnitine accumulation in capillary endothelial cells appears to up-regulate oxygen transport to exercising muscles via a vasodilatory impact on the capillary, lowering local muscular hypoxia seen during intensive exercise (34). In this investigation, serum CAT activity was lower during resting and after exercising (43). Because it is an intracellular enzyme, CAT appears to have no role in serum. Low CAT activity after exercising minimises muscle fibre and erythrocyte damage. It is found that, L-carnitine supplementation could minimise muscle damage after exercise due to low oxidative stress and CAT activity (44).

Previous research by Parandak et al. (26), Ho et al. (29), Koozehchian et al. (33), and Volek et al. (34) showed that L-carnitine supplementation increased overall antioxidant capacity and lowered MDA levels. According to Ayala et al. and Repetto et al., this phenomenon is caused by the decrease in membrane permeability and component escape by lipid peroxidation suppression, which is due to antioxidant supplementation (42, 45). Antioxidant enzyme activity can be increased to protect endothelial cells from oxidative damage (46). In other words, due to its antioxidant properties, L-carnitine may be an efficient antioxidant agent in reducing muscle injury during exercise.

The inflammation caused by muscle injury triggers the production of ROS by regulating the expression of pro-inflammatory cytokines such as IL-1, IL-6, and TNF and activating the nuclear transcription factor-B (NF-B) pathway (47-48). Antioxidants such as L-carnitine, glutathione, and astaxanthin found in previous research are able to diminish ROS production, hence inhibiting the NF-B activation cascade (49-50). These findings are consistent with those of Lee et al. (40), who found that L-carnitine supplementation of 1,000 mg per day could reduce c-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-a (TNF-a) levels in coronary artery patients after 12 weeks. After L-carnitine ingestion and moderate-intensity exercise prescription, low exposure of cell membranes to ROS has caused less sarcolemma disruption and reduced soreness in recreational weight-trained men (34) and middle-aged men and women (29). It is means that low dosage of L-carnitine is sufficient to been ingested as supplement among recreational athlete and sedentary individuals.

Regarding the safety of L-carnitine supplementation, Singh and Aslam indicated that mild side effects could happen, such as nausea and vomiting, after taking the L-carnitine supplement at a dose of 2,000 mg per day (51). Nevertheless, Lee et al. (40) reported no adverse effects in CAD patients after consuming 1,000 mg daily of L-carnitine (500 mg at two different times). Rubin et al. discovered no statistically significant changes in the liver and renal functions between the LCLT and placebo settings (17). According to the findings, LCLT may be taken as a dietary supplement and has no negative impacts on metabolic and haematological safety factors

in healthy people and patients. In addition, the Food and Drug Administration has authorised L-carnitine as a treatment for primary and secondary carnitine deficiency disorders (52). It might be extensively used as a supplement to benefit from its possible health benefits (53).

L-carnitine and its effects on exercise performance

Acute L-carnitine ingestion of 3,000 mg per day has improved aerobic and anaerobic performance in elite male artistic gymnasts (32). Gymnastics is a high-intensity exercise that will produce a high level of lactate, which affects the gymnast's performance (54). However, due to the effects of L-carnitine supplementation on acetyl-CoA stability to free CoA ratio, it could prevent lactate accumulation in the blood and indirectly affect both aerobic and anaerobic performance. Thus, L-carnitine can be recommended to gymnast athletic to improve sports performance and delay fatigue due to low lactate accumulation.

Additionally, L-carnitine consumption improves energy production by protecting tissues from oxidative damage and inflammation during exercise and enhances various metabolic pathways such as fat oxidation (6, 55). Therefore, this mechanism reduces the production of free radicals, which contributes to shorter running times among athletes (20). L-carnitine's protective effect on blood cells prevents muscle damage caused by exercise and indirectly improves time to exhaustion (56). It is supported by Orer and Guzel (36) and Burrus et al. (30), which reported prolonged time to exhaustion and decreased blood lactate levels after L-carnitine supplement ingestion.

Studies have also found that L-carnitine supplementation increases muscular strength and power in renal disease patients, healthy individuals and resistance-trained males (5, 28-30). Owen et al. (57) stated that L-carnitine supplementation has been shown to preserve amino acids that are used as a source of energy, potentially making them usable for new protein synthesis. As a result, there is less protein degradation during exercise (58). These effects could increase muscle mass in animal and human studies (58-59). In retrospect, L-carnitine can be consumed by healthy individual and also patients to improve muscle strength.

The strength of this study could be established the knowledge regarding the beneficial effects of L-carnitine supplement with recommended dosages and exercise prescriptions on overall body health in human.

Limitation

There are a few limitations of this study. Comparison of previous literatures are difficult due to limitation of studies with large scale different. It is also involves different in dosages of supplement, variations in duration, types and intensity of exercise interventions and different sample of studies. Besides, this present study only publications in English were included in this systematic review, which covers the years from 2000 to 2021. Therefore, a few relevant articles might be overlooked.

CONCLUSION

This review reports that L-carnitine suppresses oxidative stress levels due to its antioxidant capacity. It also controls metabolic responses, reduces serum lipid profiles, and promotes anti-inflammatory effects. L-carnitine is safe for healthy individuals, athletes, and patients. It also has the potential to elicit positive effects due to its essential amino acid and fatty acid content on oxidative stress, metabolic response, lipid profiles, anti-inflammatory effects, and antioxidant properties. Therefore, the types and intensities of exercise, the duration of the intervention, and supplementation dosage as well as exact time either pre, mid or post supplementation have been taken into consideration and may influence the beneficial effects of a combined L-carnitine supplement with exercise on biochemical markers and exercise performance.

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