

Pengaruh Suplementasi L-Carnitine Terhadap Berat Badan dan Persentase Massa Lemak pada Individu Gemuk/Obesitas Sehat

The Effect of L-Carnitine Supplementation on Body Weight and Body Fat Percentage in Healthy and Overweight/Obese People

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ABSTRAK

Latar belakang: Obesitas telah menjadi masalah yang serius di seluruh dunia. Meskipun kampanye dan rekomendasi terkait modifikasi gaya hidup sudah ditegakkan, tren obesitas masih cukup meningkat. Selain modifikasi gaya hidup, suplementasi makanan tampaknya memiliki efek penurunan berat badan yang menjanjikan. Salah satu suplemen makanan paling populer adalah L-Carnitine.

Tujuan: Untuk mengeksplorasi peran suplementasi L-Carnitine dalam memengaruhi berat badan, khususnya pada individu yang sehat dan obesitas.

Metode: Penelitian ini merupakan studi literatur. Sebanyak 5850 artikel muncul pada awal proses pencarian, tetapi hanya 10 studi RCT yang dipilih dalam studi ini.

Hasil: L-karnitin memiliki peran penting dalam metabolisme asam lemak rantai panjang di mitokondria. Konsumsi 500 mg sampai 1 g suplemen L-Carnitine dalam 12 minggu terbukti menurunkan berat badan di antara peserta dengan status gizi gemuk dan obesitas. Suplementasi L-Carnitine juga memiliki efek yang signifikan pada penurunan massa lemak pada subjek dengan status gizi normal dan obesitas.

Kesimpulan: Suplementasi L-Carnitine menunjukkan hasil pada penurunan berat badan dan pengurangan massa lemak terutama pada individu dengan status gizi gemuk dan obesitas yang melakukan latihan fisik dan menjalani pembatasan kalori.

Kata Kunci: L-Karnitine, suplementasi, penurunan berat badan, obesitas, massa lemak

ABSTRACT

Background: Obesity has become a serious problem worldwide. Despite established lifestyle modification campaign and recommendation, obesity trend remains increasing. In addition to lifestyle modification, dietary supplementation seemingly has a promising weight-reduction effect. One of the most popular dietary supplement is L-Carnitine.

Objectives: This study aimed to comprehend potential roles of L-Carnitine supplementation on weight loss, specifically in healthy, overweight, and obese individuals.

Methods: This is a literature review article. The search criteria retrieved 5850 articles and a total of 10 RCT studies included in the final review.

Results: L-Carnitine plays a key role in long-chain fatty acid metabolism in mitochondria. The consumption of 500 mg to 1 g of L-Carnitine supplementation within 12 weeks was shown to decrease weight among overweight and obese participants. Moreover, L-Carnitine supplementation has a significant and direct effect on fat mass reduction in subjects with normal BMI and obesity.

Conclusions: L-Carnitine supplementation may show results in weight loss and fat mass reduction especially among obese and overweight individuals who performed physical exercise and underwent calorie restricted diet.

Keywords: L-Carnitine, supplementation, weight loss, obesity, body fat

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INTRODUCTION

Obesity, as defined by a body mass index (BMI) value greater than or equal to 30 kilograms, is considered to be a global public health concern, as it affected 13% of the world's adult population in 2016 (WHO, 2020). Obesity has become a major risk factor for developing chronic degenerative disease, for instance, type 2 diabetes mellitus, certain form of cancer, endocrine dysfunction, stroke, and cardiovascular disease (Peters *et al.*, 2019). Energy imbalance resulted from excessive energy intake above the energy expenditure over a prolonged period of time has been identified as the main cause of obesity (Thavorncharoensap, 2017). The problem is accelerated with sedentary lifestyle and transition to a Western diet, that is characterized by a high amount of saturated fat, overuse of salt, and refined sugar (Barnes, 2012; Myles, 2014; Kopp, 2019).

Thus, comprehensive lifestyle modification through diet change, increased physical activity, and psychological approach is recommended as a treatment as well as a prevention strategy for obesity (Wadden *et al.*, 2012; Lean, 2015). In addition, pharmacological intervention includes over-the-counter dietary supplement may be beneficial in obesity management (Kil Joo and Sup Lee, 2011; Saunders *et al.*, 2016). This strategy is intended to achieve weight loss, and to a greater extent, normal BMI, which will significantly reduce the risk for developing obesity-associated morbidity (Lean, 2015). Weight reduction of 5-10% can manifest in cardiovascular and metabolic advantage (Pilitsi *et al.*, 2019). Recently, L-carnitine supplementation has been widely used during the past 30 years and is considered as a potential obesity intervention because of its biological properties (Sahlin, 2011). Nevertheless, the health implication of L-carnitine has not yet been investigated, hence future research must be taken to analyze the efficacy of prolonged administration of L-Carnitine.

L-Carnitine is a non-essential amino acid derivative which plays a key role in lipid metabolism as a carrier which facilitates the transportation of long-chain fatty acid across the inner mitochondrial membrane for subsequent β -oxidation (Reuter and Evans, 2012; Gropper, Sareen S. Smith, 2013; D'Antona *et al.*, 2014). L-Carnitine also enhances triglyceride utilization from adipose tissue to produce energy (Leelarungrayub *et al.*, 2017). In glucose metabolism, carnitine modulates the acetyl-CoA/CoA ratio and pyruvate dehydrogenase activity which may lead to a decrease in acetyl-CoA and activation of glycolytic pathway (Bene, Hadzsiev and Meleghe, 2018). It is also responsible for improving insulin resistance and diminished appetite (Padmavathi and Vishwa, 2012; Pooyandjoo *et al.*, 2016; Gnoni *et al.*, 2020; Talenezhad *et al.*, 2020). These mechanisms are thought to increase energy expenditure which underlies the reason for the wide use of carnitine supplements in weight loss program.

Numerous clinical trials have indicated inconsistent results of L-carnitine on weight loss. Previous meta-analysis studies conducted by Askarpur (2020), Talenezhad (2020), and Pooyandjoo (2016) have reported that L-carnitine supplementation resulted in weight reduction. However, other studies have shown that there is no significant effect of this supplement (Villani, R.G., Gannon, J., Self, M., Rich, 2000; Elmslie *et al.*, 2006). The aim of this literature review is to evaluate the potential effect of L-carnitine supplementation on weight loss.

METHODS

The literature search was carried out on clinical trial research articles using electronic database, namely Scopus, Science Direct, PubMed/Medline, Clinical Trial, and Google Scholar. The following keywords were used during the comprehensive research, "L-Carnitine Metabolism", "L-Carnitine Role in Lipid Metabolism", "L-Carnitine Deficiency", "Effect of L-Carnitine Supplementation on Weight Loss", "L-Carnitine Supplementation for Obesity", "Randomized Controlled Trial of L-Carnitine", "Pharmacotherapy for Obesity". Selected studies must meet the following eligible criteria; (i) conducted on healthy or overweight/obese adults with no comorbid, (ii) a randomized controlled trial of L-Carnitine supplementation which provided a comparison between the intervention group and placebo. Based on the inclusion criteria, a total of 5 selected RCT studies were included in this literature review and will be presented in Table 1. Data extracted from the studies include last name of first author, year of publication, methods, population, and the research outcome

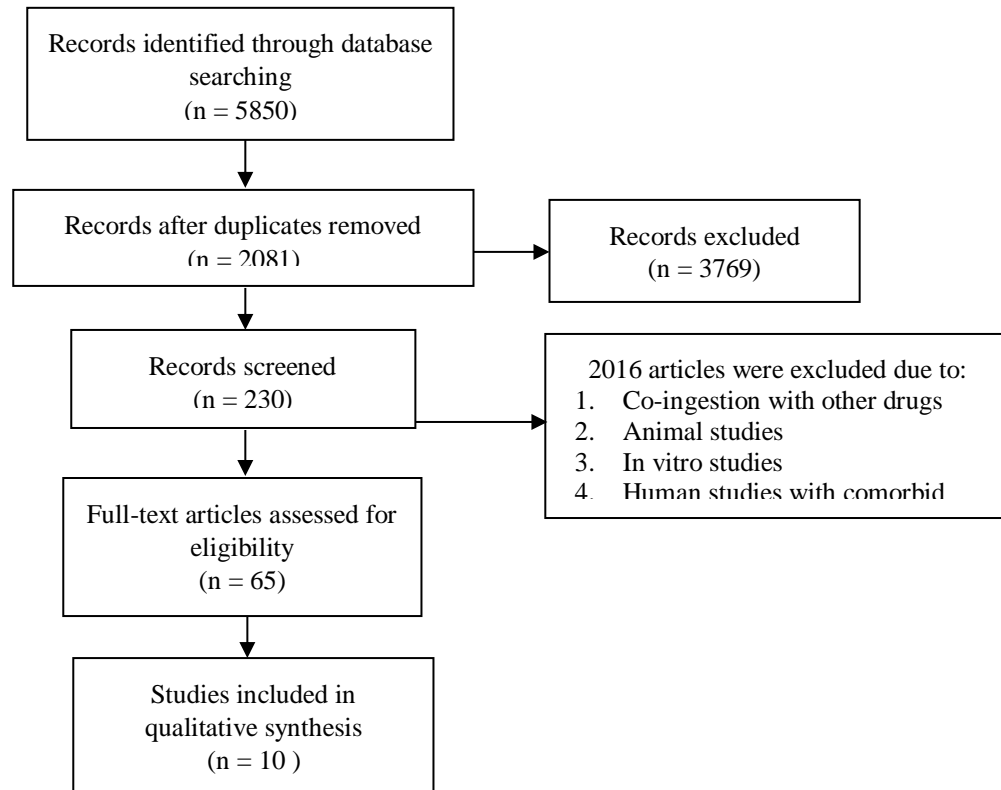


Figure 1. PRISMA study flow diagram

RESULT AND DISCUSSION

Carnitine Metabolism

L-carnitine can be naturally produced in the human body, utilizing lysine and methionine as the precursor (Flanagan *et al.*, 2010). The first reaction in the synthesis process is the N-methylation of lysine with S-adenosyl methionine (SAM), a compound made from methionine oxidation (Strijbis, Vaz and Distel, 2010). This process is catalyzed by lysine methyltransferase to generate 6-N-trimethyllysine (TML) (D'Antona *et al.*, 2014). TML subsequently undergoes hydroxylation via trimethyllysine hydroxylase to yield 3-OH trimethyllysine. In this reaction, ascorbate acid and iron act respectively as a coenzyme and a cofactor for trimethyllysine hydroxylase (Reuter and Evans, 2012). The formed 3-hydroxytrimethyllysine is simultaneously metabolized to form γ -butyrobetaine and ultimately transformed into carnitine (Gropper, Sareen S. Smith, 2013).

In mammals, carnitine biosynthesis occurs primarily in liver and kidney (Pekala *et al.*, 2011). Other tissues, that do not comprise enzymes required to synthesize L-carnitine, get L-Carnitine from the bloodstream through active transport (Flanagan *et al.*, 2010; Pekala *et al.*, 2011). However, skeletal and myocardial muscles represent the major carnitine pool which account for about 95% of total carnitine, whereas the remaining part stored in the liver, kidneys, and plasma (Gnoni *et al.*, 2020). About 75% of total carnitine in the human body derived from dietary source and 25% from *de novo* biosynthesis (Shekhawat, P.S., Sonne, S., Carter, A.L., Matern, D., Ganapathy, 2013). Renal tubular reabsorption is essential for maintaining carnitine homeostasis in the body, with > 90% carnitine is being reabsorbed in the kidney (Reuter and Evans, 2012). Carnitine synthesis rate in the adult human body is approximately 160-480 $\mu\text{g}/\text{kg}$ body weight (Reuter and Evans, 2012). However, this rate decreased in certain circumstance, such as stress and physical exertion (Strijbis, Vaz and Distel, 2010).

Animal-based products including red meat, dairy products, poultry, and fish are the main source of L-carnitine (Odle, Adams and Vockley, 2014). Carnitine is found in lower concentration, and to lesser extent, absent in plant origin diet (Fielding *et al.*, 2018). Therefore, a strict vegetarian may possess carnitine insufficiency and may require additional L-carnitine supplement. Carnitine is absorbed from diet approximately at a range of 54 to 87% in the proximal small intestine by sodium-dependent active transport (Gropper, Sareen S. Smith, 2013). The unabsorbed residues will subsequently be degraded by gut microbiota in the large intestine (Koeth *et al.*, 2013).

Some studies demonstrated that carnitine obtained from dietary consumption has higher bioavailability compared with oral supplement ingestion (Zhang *et al.*, 2019). Bioavailability of carnitine in individual who consumed low-carnitine diet is approximately 75%, meanwhile in individual who consumed high-carnitine diet

is merely 63% (Rebouche, 2004). The bioavailability of 2 g oral L-carnitine is at a range of 9-25%, and the bioavailability decreases in 6 g oral L-carnitine, which is solely 4-6%. This indicated that carnitine absorption might be influenced by diet composition as well as organic cation transporter 2 (OCTN2) saturation in the enterocytes (Wang *et al.*, 2020). It is estimated that carnitine is saturated with intakes of about 2 g (Gropper, Sareen S. Smith, 2013).

How L-Carnitine Supplementation Affects Weight Loss and Fat Mass Reduction in Healthy, Overweight, and Obese Individuals

Obesity is a state of excess accumulation of body fat (Kumar, Abbas and Aster, 2017). This can lead to the occurrence of metabolic syndrome, a cluster of condition including abnormal cholesterol level, increased fasting plasma glucose, abdominal obesity, and raised blood pressure (Rochlani *et al.*, 2017). Various strategies have been established to combat obesity epidemic, yet the obesity incidence is still increasing. The prevalence of overweight and obesity is projected to be 1.35 billion and 573 million individuals, respectively (Kelly *et al.*, 2008). Beside lifestyle modification, alternative choice in supplementation has been widely considered. L-carnitine is one of the most popular dietary supplementation that has been approved by Food and Drug Administration (FDA) and has a promising weight-reduction effect. L-Carnitine supplement is mainly used for treating hemodialysis patients in order to replenish carnitine depletion in the body (Askarpour *et al.*, 2020).

The exact mechanism of how L-Carnitine affects body weight remains unclear, but several suggestions have been proposed to explain the possible mechanism. L-Carnitine has been known to play a key role in lipid metabolism, specifically β -oxidation, which takes place in the mitochondria, as it increases the metabolism (Reuter and Evans, 2012). The first step in lipid catabolism is an activation of fatty acid by binding to CoA-SH via acyl-synthetase before oxidation (Kumari, 2018). The mitochondria membrane is impermeable to CoA substance, hence activated fatty acid must bind to carnitine to move across the outer mitochondria membrane (Sargowo, no date; Schulz, 2013). This reaction is catalyzed by carnitine acyl-transferase I which located at the outer mitochondria membrane (Sahlin, 2011). Another enzyme called carnitine translocase will subsequently enable transportation of acyl-CoA across the inner mitochondria membrane. Within the mitochondria, acyl-CoA will undergo β -oxidation and form acetyl-CoA which can simultaneously enter Krebs cycle for produce ATP production.

Furthermore, there is an enzyme called carnitine octanoyltransferase (COT) that depends on carnitine which has important roles in β -oxidation of very long-chain fatty acid, α -oxidation of phytanic acid, a branched-chain fatty acid which can be obtained through diet. In experimental mice study, L-carnitine was observed as an inducer of expression peroxisome proliferator-activated receptors- γ (PPARs- γ) expression at the mRNA and protein levels. PPARs- γ was known to prevent fatty acid synthesis in the liver of cachectic mice, and might reduce serum tumor necrosis factor α (TNF- α). However, a precise and proper study in human-setting should be addressed to confirm this mechanism.

Table 1. The Effects of L-Carnitine Supplementation on Weight Loss

| Study | Population | Methods | Result |
|--|--|--|---|
| Sawicka, <i>et al.</i> , 2018 (Sawicka <i>et al.</i> , 2018) | Twenty-two (22) women aged 65-70 year in Poland. | Design: Randomized double-blind trial Intervention: Women in intervention group took 1500 mg of L-Carnitine/day, whereas women in control group received isonitrogenous placebo/day. Duration: 24 weeks. | The study revealed that the supplementation has no effect on participants' body weight. |

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| Mosah, <i>et al</i> , 2015(Mosah <i>et al.</i> , 2015) | Sixty (60) obese women aged 20-40 years with BMI \geq 30 kg/m ² with no comorbid. | Design: Randomized single-blind trial Intervention: Participants in Intervention group took 1000 mg of L-Carnitine capsule, meanwhile participants in control group received no treatment. Duration 12 weeks | There is 7.38% weight reduction in intervention group, whereas the mean percentage of weight reduction in controlled group is merely 3.79%. |
| Rafraf, <i>et al</i> , 2015(Rafraf, M., Karimi, M., Jafari, 2015) | Forty-four (44) obese non-pregnant women, with BMI \geq 30 kg/m ² , body fat percentage \geq 30, with no comorbid (cardiac ischemia, liver, cardiovascular disease, kidney or gastrointestinal disease, hypo/hyper-thyroidism, orthopedic disease, rheumatoid arthritis, diabetes mellitus, and hypertension). | Design: Double-blind randomized controlled trial Intervention: Intervention group is divided into 2 groups, namely: Group 1, 2 g of L-Carnitine supplements (eight 250-mg tablets/day) Group 2, 2 g of L-Carnitine supplements (eight 250-mg tablets/day) + aerobic training Control group is divided into 2 groups, namely: Group 3, eight placebo tabs contained lactose and aerobic training Group 4, eight placebo tabs contained lactose Duration: 8 weeks | <ol style="list-style-type: none"> 1. There is no significant weight reduction in two intervention groups, neither significant differences between intervention and control groups. 2. Weight reduction percentage in group 1, 2, and 3 is 0,44%, 0,1%, 0,82%, respectively. |
| Alshammari, 2011(Alshammari, 2011) | Twenty (20) obese women aged 50-55 years with BMI \geq 30 kg/m ² | Design: Randomized controlled trial Intervention: Subjects in intervention group took 4 mg/kg body weight of L-carnitine and did physical exercise, whereas subjects in control group solely did physical exercise. Duration: 8 weeks | There is a significant weight loss in both groups with a greater amount of 17.9 kg reduction in the intervention group. |
| Wall, <i>et al</i> , 2011(Wall <i>et al.</i> , 2011) | Fourteen (14) healthy, who train 3-5 times per week with mean BMI 23 (classified as normal) in the UK. | Design: Randomized double blind trial Intervention: Volunteers in intervention group ingested 2 gram of L-Carnitine supplementation and 80 gram of CHO + exercised. Meanwhile in control group, volunteers merely received 80 g of CHO + exercise. Duration: 24 weeks | There is no significant weight reduction detected. |

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|--|---|--|---|
| Odo, <i>et al</i> , 2013(Odo, Tanabe and Yamauchi, 2013) | 97 overweight (BMI: 25-28 kg/m ² , triglyceride: 150-350 mg/dL, waist circumference: 85-100 cm) men with no regular exercise habit in Japan. | Design: Randomized double blind study Intervention: Group 1: 500 mg L-Carnitine supplementation + exercise + reduced calorie intake Group 2: 500 mg L-Carnitine supplementation Group 3: exercise + reduced calorie intake Group 4: no intervention Duration: 4 weeks | There is a significant weight reduction in group 1. |
|--|---|--|---|

Daily L-Carnitine administration with a dose equal to or less than 2 gram within 6 months is thought to effectively result in weight reduction (Pooyandjoo *et al.*, 2016). A meta-analysis by Talenezhad (2020) showed that supplementation of L-Carnitine could reduce respectively 1.53 kg and 1.29 kg in overweight and obese participants (Talenezhad *et al.*, 2020). This weight reduction was even greater in studies with follow up period of > 12 weeks (Talenezhad *et al.*, 2020). A study conducted by Mosah (2015) reported a weight reduction in healthy obese women from single 12-week L-Carnitine supplementation (1 gram/day). Alshammari (2011), on the other hand, showed a similar result, but with the 8-week 4 mg/kg body weight L-Carnitine supplementation and the addition of 150 minute exercise per week along with the supplementation. Despite the occurrence of weight loss in the intervention group, a study conducted by Rafraf (2015) has shown that participants in control group also underwent a non-significant weight reduction.

This may be due to its ability to stimulate energy expenditure through beta-oxidation of long-chain fatty acid, decrease of acetyl-CoA/CoA ratio which subsequently reduces acetyl-CoA concentration and further induces the carbohydrate utilization (Mosah *et al.*, 2015). This was confirmed by Wutzke and Lorenz (2004) who found an increased fat oxidation and an improved dietary fat utilization in overweight subjects (Wutzke and Lorenz, 2004). Furthermore, acetylcarnitine, may have a metabolic property to improve glucose homeostasis (Bruls *et al.*, 2019). A prior study showed that L-carnitine supplementation, along with calorie restriction, improves insulin sensitivity in impair glucose tolerance (IGT) patients. This finding was in agreement with a clinical trial performed by Samimi *et al* (2016) which stated that L-carnitine could decrease HOMA-IR in diabetic and polycystic ovary syndrome (PCOS) patients, respectively (Samimi *et al.*, 2016; Xu *et al.*, 2017).

Moreover, increased serum adiponectin was detected in participants who ingested 500 mg L-Carnitine supplementation (Odo, Tanabe and Yamauchi, 2013). Adiponectin, the so-called “fat-burning molecule”, can stimulate fatty acid oxidation in muscle, improve insulin sensitivity of liver and muscle and other target organs, as well as regulate peripheral glucose metabolism, which ultimately induce decreased body weight (Fornyo-Germano, De Felice and Do Nascimento Vieira, 2019). Serum adiponectin may alter in obese people (Gariballa *et al.*, 2019). Accumulation of visceral fat which primarily consists of white adipose tissue can increase adipokines production which interfere with adiponectin level (Achari and Jain, 2017).

However, supplementation may solely be effective in obese or overweight individuals (Askarpour *et al.*, 2020; Sawicka, Renzi and Olek, 2020). Several studies demonstrated no significant change in subjects with BMI less than 25 kg/m², that is categorized as normal. A study by Sawicka (2018) showed that 1.5 g L-Carnitine per day did not affect weight in elderly women with normal BMI. In addition, this finding is in concordance with a study by Wall who showed that L-carnitine supplementation did not have weight-reduction effect among healthy recreational athlete who performed training 3-5 times a week. Nonetheless, despite no weight change, Wall found an increased lipid metabolism as an effect of L-carnitine supplementation in physically active respondents.

Table 2. The Effects of L-Carnitine Supplementation on Body Fat Reduction among Healthy Subjects

| Study | Population | Methods | Result |
|--|--|---|---|
| Mot, <i>et al</i> , 2018(Mor <i>et al.</i> , 2018) | Sixteen (16) male athletes aged 18-28 years in Turkey. | Design: Randomized controlled trial Intervention: Intervention group was given 1 g L-Carnitine supplement/day prior to regular training, whereas control group was | Decreased body fat percentage was reported in intervention group. |

| Study | Population | Methods | Result |
|---|--|--|---|
| | | given placebo. Duration: 7 days | |
| Stack, 2017(Stack, 2017) | Seven (7) recreationally-trained female runners between the ages of 19 and 22 years. | Design: Randomized controlled trial Intervention: L-Carnitine group: 1.3 g carnitine powder + physical exercise L-Carnitine + Carbohydrate (LC + CHO) group: 1.3 g carnitine powder and 10 g dextrose powder + physical exercise Duration: 8 weeks | There is a decreased fat mass percentage in group 1 |
| Dominguez, <i>et al</i> , 2015(Turck <i>et al.</i> , 2018) | Twenty-four (24) male soccer players aged \geq 18 years in Mexico. | Design: Double-blinded clinical trial Intervention: Participants in intervention group ingested 3 g/day L-Carnitine, meanwhile participants in control group was given placebo three times a day Duration: 30 days | There is no change in the percentages of body fat in both intervention and control group. |
| Karimi <i>et al</i> , 2013(Karimi <i>et al.</i> , 2013) | Forty-four (44) obese women in Iran. | Design: Randomized controlled trial Intervention: Participants were assigned into 4 groups: Group 1: 2 g of L-Carnitine supplementation/day Group 2: merely training + placebo Group 3: 2 g of L-Carnitine/day + training Group 4: placebo Duration: 8 weeks | The supplementation alone and the combination with training can decrease fat percentage significantly |
| Haghihi, <i>et al</i> , 2010(Haghighi <i>et al.</i> , 2010) | Eighteen (18) active men aged 33-58 years in Iran | Design: Semi-experimental study Intervention: Participants in intervention group performed aerobic training and consumed 10 mg/kg body weight L-Carnitine/day, meanwhile participants in control group received 2.5 mg/kg body weight B1 vitamin as placebo. Duration: 6 weeks | Aerobic training and L-Carnitine supplement significantly reduce boy fat percentage. |

On the other hand, some evidences suggested that L-Carnitine supplementation could decrease body fat percentage. Four out of five studies suggested fat mass reduction among both obese and individuals with normal BMI. The mechanism underlies this effect was the ability of L-Carnitine in enabling fat oxidation. However, five studies which examined L-Carnitine supplementation effects on weight loss included in this literature review showed inconsistent result. Three out of five studies demonstrated weight reduction among overweight and obese individuals, meanwhile the effect did not show in healthy active subjects. This study is limited by small numbers of studies conducted in healthy, overweight and obese with no comorbid other aspects including varied design, intervention method, supplementation protocol, and different characteristics among participants of the analyzed studies. Hence, definitive recommendations regarding L-Carnitine supplementation require future investigation.

CONCLUSION

L-carnitine has an important role in β -oxidation as a carrier which transports acyl-CoA across the mitochondria membrane. Moreover, L-Carnitine can also reduce acetyl-CoA/CoA ratio to activate glycolytic pathway and play important role in inducing PPARs- γ gene expression. Nevertheless, the evidence of weight-loss effect in L-Carnitine supplementation remains insufficient. This study found that 500 mg to 1 g of L-Carnitine supplementation within 12 weeks was shown to decrease weight among overweight and obese participants. L-Carnitine supplementation also has significant and direct effect on fat mass reduction in both healthy and obese subjects. However several studies suggested that this weight loss and fat mass reduction effect could be more effective in subjects who performed physical exercise and underwent calorie restricted diet.

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