

## Review Article

# The anti-wasting effects of L-carnitine supplementation on cancer: experimental data and clinical studies

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**Background and Objectives:** Cachexia is a paraneoplastic syndrome that affects the large majority of patients with end-stage cancer. No known therapy exists to effectively overcome the severe symptoms of cachexia, which include anorexia, weight loss and fatigue. This study considered the results of both experimental and clinical studies to evaluate the suitability of L-carnitine and its derivatives as potential therapies for cachexia in patients with cancer. **Methods and Study Design:** All available English-language papers on the use of L-carnitine in patients with cachexia related to cancer, including reviews, case reports, case series, and clinical trials, were obtained by searching multiple databases, including all Elsevier publications, Web of Knowledge, PubMed, Scopus, clinical trials, and the Cochrane database of systematic reviews. **Results:** The protective effects of L-carnitine were extracted from the literature review based on critical mechanisms involved in skeletal muscle loss, including increased proteolysis, impaired protein synthesis, myonuclear apoptosis, oxidative stress, and mitochondrial dysfunction. The results of this process favored L-carnitine supplementation in patients with cancer-related cachexia. Nitrogen balance was improved either through the increase of protein synthesis or by reduction in proteolysis, inhibiting apoptosis or reversing inflammatory processes. **Conclusions:** Although clinical studies are inconclusive, studies in animal models support L-carnitine administration to prevent oxidative stress and ameliorate mitochondrial function. L-carnitine supplementation leads to beneficial effects on several critical mechanisms involved in pathologic skeletal muscle loss and improved fatigue-related parameters in patients with cancer. However, more well-designed, double-blinded, randomized clinical trials are necessary to establish L-carnitine supplementation as a therapeutic strategy for cachexia.

**Key Words:** L-carnitine, muscle wasting, cachexia, fatigue, oxidative stress

## INTRODUCTION

### *L-carnitine and derivatives*

L-carnitine (LC;  $\gamma$ -trimethylamino- $\beta$ -hydroxybutyrate) is a naturally endogenous quaternary amine that is essential for normal function of mammalian cells. This water soluble substance has several well-known derivative esters, including acetyl-L-carnitine (ALC), propionyl-L-carnitine (PLC), and palmitoyl-L-carnitine.<sup>1</sup> The main sources of LC and its derivatives are dietary, especially meat and dairy products, and to a lesser extent, endogenous biosynthesis,<sup>2</sup> which is performed mainly in the liver and kidneys.<sup>3,4</sup> A low-level of exogenous LC intake occurs in strict vegetarians and has minor effects on plasma because of the efficient compensation of renal reabsorption.<sup>5</sup> Consumption of high doses of LC supplements inhibits the activity of c-butyrobetaine dioxygenase, which catalyzes during the last phase of the LC biosynthesis cascade. However, this inhibition does not interfere with endogenous carnitine synthesis because the activity of c-butyrobetaine dioxygenase is not rate-limiting for endogenous synthesis.<sup>6,7</sup> The most important function of LC and its derivatives is the importation of long-chain fatty

acids from cytosol into mitochondria to facilitate  $\beta$ -oxidation and acetyl Coenzyme (CO) A production during the tricarboxylic acid cycle.<sup>8</sup> LC also plays a role in the efflux of accumulating acyl groups, such as acyl-carnitines, outside of mitochondria and cells. During the regulation of free CoA, LC regulates the activity of the pyruvate dehydrogenase complex, which is a key metabolic enzyme;<sup>9</sup> LC deficiency is associated with impaired fatty acid and glucose utilization as well as insulin sensitivity.<sup>10</sup>

LC potentiates the activity of antioxidant enzymes, including glutathione peroxidase, catalase, and superoxide dismutase (SOD), and chelates with metal ions during

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reactive oxygen species (ROS) generation. Antioxidant effects of LC are comparable to other antioxidant agents, such as alpha-tocopherol.<sup>1</sup> LC deficiency is diagnosed based on plasma levels, although these may not accurately reflect tissue concentrations. In clinical settings, a plasma-free LC of 201 mol/L or less indicates deficiency, while an acyl-free LC ratio of 0.4 or greater represents depletion of free LC due to increased acyl CoA derivatives.<sup>11</sup> Several studies have found that clinical conditions of LC deficiency, such as cardiomyopathy or skeletal myopathy, occur when tissue LC are 10–20% lower than normal values,<sup>12</sup> and deficiency itself is defined as a decrease of intracellular LC that causes acetyl CoA ester accumulation and mitochondrial inner transporter inhibition. When LC is not present during mitochondrial oxidation of fatty acids, liver and heart failure may occur.<sup>13</sup>

For example, LC deficiency may induce cardiomyopathy due to failure of mitochondrial dysfunction and acetyl CoA metabolism. Cardiomyopathy is treatable by dietary supplementation. While the cause of cardiomyopathy is still unclear, determination of plasma carnitine and carnitine supplementation of hypocarnitinemic patients is of great therapeutic modalities.<sup>14</sup> Primary LC deficiency is a rare condition characterized as a genetic abnormality in the transport or biosynthesis of LC. But secondary LC deficiency is inducible by viral attack or drug consumption.<sup>14</sup>

Past studies have shown that administration of LC supplements improves several health indicators in patients with chronic diseases such as cancer,<sup>15</sup> chronic kidney disease (CKD),<sup>16,17</sup> human immunodeficiency virus (HIV), hepatitis C,<sup>18</sup> or hepatic encephalopathy.<sup>19</sup> These improvements are seen in quality of life indices, nutrition and condition of the body, symptoms related to fatigue, and oxidative stress and inflammation. Recently, an animal study has shown that LC improves proteolysis in skeletal muscles, enhances muscle weight, and increases physical performance parameters in rats with induced tumors.<sup>20</sup> Reduction in plasma LC has been reported in chronic diseases such as cancer, HIV, and CKD.<sup>21–23</sup>

Plasma deficiency in chronic disease is due to food intake restriction, which is accompanied by decreases in dietary uptake of LC and certain micronutrients (vitamin C, vitamin B-6, and iron), which are consumed as cofactors for LC synthesis. During chemotherapy regimens, LC deficiency will be induced, because of failure in LC absorption and synthesis and/or increase in urinary LC excretion by chemotherapy agents.<sup>24,25</sup> This review summarizes the results from experimental and clinical studies that examined the effects of supplements of LC or its derivatives on pathologic skeletal muscle loss (cachexia) and related complications in cancer patients. We focused on evidence that exists in either patients with cancer or animal models, excluding the effects of LC and its derivatives on other pathological conditions such as hemodialysis, hepatitis, and HIV.

### ***L-carnitine and cancer cachexia***

Cancer cachexia, or severe loss of skeletal muscle mass, is a severe inflammatory metabolic syndrome. This syndrome is characterized by extensive loss of adipose tissue and skeletal muscle. Fatigue and impairment of normal

activities or quality of life are common complications of muscle wasting, and can eventually progress to death. Cancer cachexia occurs in more than half of patients with cancer.<sup>26</sup> The loss of muscle mass associated with loss in body weight is the main feature of this syndrome.<sup>27,28</sup>

The pathogenesis of muscle wasting is not completely understood; however, an imbalance between protein catabolism and protein anabolism in muscles has been suggested. Several mechanisms underlying skeletal muscle loss under pathologic conditions have been postulated, including stimulation of protein degradation, impairment of protein synthesis, induction of myonuclear apoptosis or inflammation, and oxidative stress and impairment of mitochondrial function.<sup>29</sup>

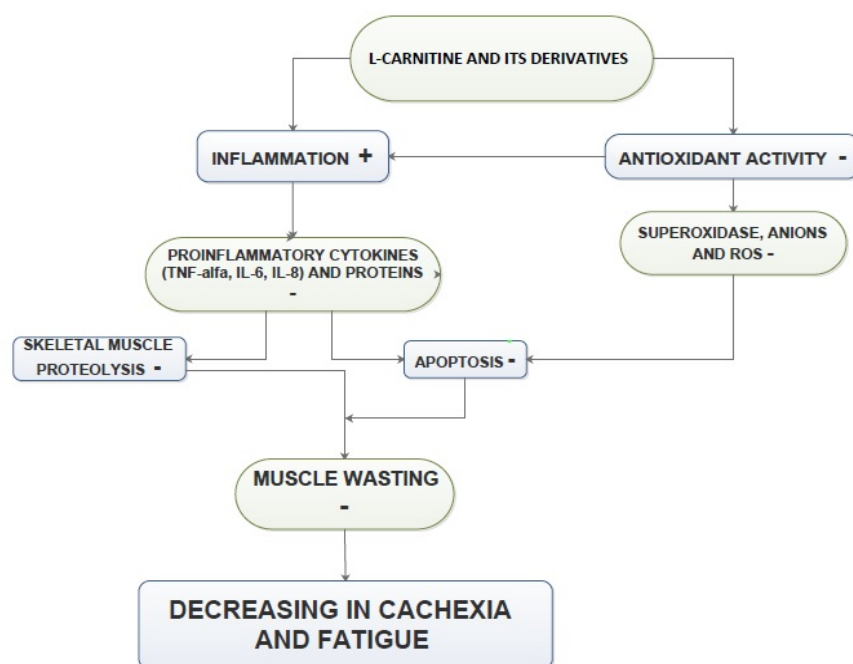
Multiple pro-inflammatory factors, such as interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)- $\alpha$ , c-reactive protein (CRP), and proteolysis inducing factor (PIF), protein catabolic pathways, particularly the ubiquitin-proteasome system (UPS), are systemically activated during the muscle-wasting process.<sup>30,31</sup> Because ROS are potent inducers of the UPS, oxidative stress induced by decreased antioxidant capacity plays an important role in the development of muscle wasting.<sup>32</sup> During inflammatory conditions, generation of ROS or pro-inflammatory mediators leads to skeletal muscle apoptosis (myonuclear apoptosis) and muscle atrophy. Protein anabolism is disturbed during muscle wasting, either due to decline in the level of anabolic hormones, such as growth factor-1 and testosterone or tissue sensitivity reduction to anabolic hormones (e.g., insulin resistance). Also the negative effects of PIF and other cytokines on protein translation are initiated.<sup>33,34</sup> The degenerative impact of muscle loss on cancer can affect patient prognosis and quality of life; thus, the development of efficacious treatment modalities to overcome muscle wasting is important. To combat this, LC can be used as a suitable supplement for anti-wasting therapies in cancer patients.<sup>20</sup> Additionally, the majority of LC quantities are primarily in skeletal muscles.<sup>35</sup> It has been suggested that LC and its derivatives can be used to prevent skeletal muscle loss in cancer patients.

The proposed mechanisms underlying the beneficial effects of LC and its derivatives on mitochondrial function are based on stabilization of mitochondrial membrane by lipids/phospholipids synthesis and reduction in the amount of free long-chain fatty acids;<sup>36–38</sup> in addition, preserving the activities of key mitochondrial enzymes in energy metabolism and oxidative phosphorylation and also anti-inflammatory and anti-oxidative properties have been reported.<sup>39–41</sup>

As summarized in Figure 1, LC supplementation under pathologic conditions has several protective effects against mechanisms involved in skeletal muscle loss. These mechanisms can account for the anti-catabolic effects (increases in body mass index (BMI) and lean body mass) and the improvement of fatigue-related parameters following LC supplementation in patients with chronic diseases, such as CKD due to cancer,<sup>42</sup> hepatitis C, and hepatic encephalopathy.<sup>18,19</sup>

### ***L-carnitine and inhibition of protein degradation and apoptosis in muscles***

A recent animal study suggested that LC supplementation



**Figure 1.** The protective mechanisms of LC in skeletal muscles

may be an efficient modality for a multi-targeted therapy to treat cancer-related cachexia.<sup>20</sup> The authors showed that LC administration (1 g/kg body weight per day, for 6 days) in rats bearing AH-130 Yoshida ascites hepatoma, which is a highly cachectic rat tumor cell, resulted in significant improvement of food intake (a 15% increase) and increased skeletal muscle weight, including the gastrocnemius, extensor digitorum longus (EDL), and soleus. The treatment protocol led to a down-regulation of atrogin-1 and Muscle Ring-finger protein-1 (MuRF1), both are two gene productions, and other components, such as ubiquitin, which is a C8 proteasome subunit of the UPS. In vitro evaluations found that proteasome activity and the proteolytic rate were reduced in gastrocnemius muscles and in isolated EDL muscles, respectively, and LC administration decreased the pro-apoptotic marker, caspase-3, in the skeletal muscles of tumor-bearing rats. Caspase-3 is a protein that interacts with caspase 8 and caspase 9; all caspases play a primary role in cell apoptosis.<sup>20</sup>

In addition, physical performance (including total physical activity, mean movement velocity, and total travelled distance in a given time period) improved with LC supplementation in rats. This study suggested that LC treatment has positive effects when used to address muscle wasting not only by reducing the activity of the UPS but also by inhibiting the degradation of actomyosin complexes and muscle integrity.

Ultimately, LC treatment resulted in a significant decrease in proteasome activity by ameliorating the muscle mRNA content for ubiquitin (28%), C8 proteasome subunit (28%), and MuRF-1 (46%). No effects on other proteolytic systems (such as calcium-dependent or lysosomal protease systems) were observed.<sup>20</sup> Data currently are lacking concerning the effect of LC on proteolytic pathways in those with cancer; its anti-proteolytic and anti-apoptotic properties remain to be proven in well-designed clinical trials.

#### ***L-carnitine and inhibition of inflammation in muscles***

Several studies have shown the anti-inflammatory effects of LC supplementation in pathologic conditions. For example, LC administration (500 mg/kg for five consecutive days) prevented methotrexate-induced serum TNF- $\alpha$  in a rat model.<sup>43</sup> Şener et al induced sarcoma by implanting methylcholanthrene in rats and found that LC supplementation (200 mg/kg per day) decreased the plasma cytokines (IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ) and ameliorated cancer cachexia by attenuating cytokine production and increasing the clearance of cytokines.<sup>44</sup> In an in vivo study using an methylcholanthrene (MCA)-sarcoma-bearing rat model for cancer cachexia, administration of PLC (250 mg/kg per day) attenuated the plasma inflammatory cytokines, such as IL-1 and IL-6, compared to a control.<sup>45</sup> In a similar manner, Liu et al. demonstrated that LC supplementation (18 mg/kg per day, orally) ameliorated the plasma inflammatory cytokines, such as IL-6 and TNF- $\alpha$ ,<sup>46</sup> and attenuated serum carnitine and expression of carnitine palmitoyltransferase, which is the main enzyme in fatty acid production, in cancer cachectic mice.

Cytokines play a key role in cancer cachexia and protein catabolism by modifying cytokine action using agents that may inhibit protein wasting in skeletal muscles.<sup>47</sup> In an interim analysis of a phase III randomized study that assessed the most effective treatments for cancer-related anorexia, cachexia syndrome, and oxidative stress, LC administration did not provide significant improvements based on the plasma levels of identified pro-inflammatory cytokines (IL-6, TNF- $\alpha$ , and IL-1). In this study, 125 advanced-stage cancer patients received polyphenols and antioxidant agents, such as  $\alpha$ -lipoic acid, carbocysteine, and vitamins A, C, and E, at the beginning of the trial, before randomization into five groups: 1) medroxyprogesterone acetate/megestrol acetate; 2) pharmacologic nutritional support containing eicosapentaenoic acid; 3) LC ad a dose of 4 g/d; 4) thalidomide; and 5) medroxyprogesterone acetate/megestrol acetate, pharma-

colitic nutritional support, LC, and thalidomide for four months. Primary endpoints of the study were increase in lean body mass, decrease in resting energy expenditure, increase in total daily physical activity, decrease in levels of IL-6 and TNF- $\alpha$ , and improve in fatigue. The results showed that despite a lack of anti-inflammatory effects, LC supplementation provided significant improvements in nutritional variables and fatigue symptoms.<sup>15</sup>

In 2010, a combination regimen was found to be the most effective treatment for all primary efficacy and secondary endpoints, such as appetite, levels of IL-6, Glasgow prognostic scores, and eastern cooperative oncology group performance status scores.<sup>48</sup> A similar study investigated the efficacy and safety of LC supplementation (6 g/day for four weeks) in patients who had advanced cancer for reported fatigue, high blood levels of ROS, or both. Patients' fatigue and quality of life were measured using standard questionnaires, and oxidative stress, nutritional status, and laboratory variables, including ROS, glutathione peroxidase, and pro-inflammatory cytokines, were measured as the primary endpoints. The results supported LC treatment because fatigue, measured using the multi-dimensional fatigue symptom inventory, decreased significantly, and quality of life and nutritional variables, such as lean body mass and appetite, improved. However, significant improvement in the levels of ROS, glutathione peroxidase, or other pro-inflammatory cytokines was not substantiated.<sup>42</sup>

Madeddu et al (2011) designed a phase III, randomized trial to compare a two-drug combination including LC (4 g/day) with celecoxib (300 mg/day) or LC (4 g/day) with celecoxib (300 mg/day) and megestrol acetate (320 mg/day) to treat cancer-related cachexia. Sixty patients were eligible and pretreated with polyphenols and vitamin E, A, and C. The results showed a significant improvement in lean body mass, total daily physical activity, and physical performance, which was tested based on grip strength and a six-minute walking test. The researchers also assessed inflammatory factors, including fatigue, resting energy expenditure, body weight, and appetite, and all parameters were ameliorated in both treatment groups without any inferiority.<sup>49</sup>

#### ***L-carnitine and prevention of oxidative stress in muscles***

Evidence has been obtained in several animal models related to the preventive effects of LC supplementation in oxidative stress under pathological conditions.<sup>50,51</sup> In a review published by Moghaddas et al, the beneficial effects of LC and its derivatives against ischemia/reperfusion (I/R) injury and oxidative stress were comprehensively assessed.<sup>1</sup>

Breitkreutz et al performed a randomized, double-blinded clinical trial to evaluate the effects of 2-g daily oral LC on mitochondrial integrity and function, glutamate transport, and plasma glutamate in patients with cancer. To evaluate changes in the intracellular glutathione (GSH) and glutamate levels of the skeletal muscle tissue, part of the study was conducted in tumor-bearing mice. In the mouse model, LC administration (i.p. 1 mg/day for 28 days) led to reductions in glutamate and GSH levels in muscles as well as an increase in plasma glutamate. Clinically, the group given LC supplements

exhibited a significant reduction in plasma glutamate, with an insignificant increase in glutamate uptake in the lower extremities. The effects of LC on intramuscular GSH levels are potentially useful in clinical therapy.

The potential therapeutic effects of LC (especially over longer treatment periods) merit further investigation. However, due to the substantial decrease in intramuscular glutamate and GSH muscle tissue of tumor-bearing mice, the authors of this paper asserted that higher doses of LC (i.e., 250 mg/kg/day) do not provide additional therapeutic benefit.<sup>50</sup>

On the other hand, PLC inhibited cisplatin-induced cardiomyopathy in a rat model.<sup>52</sup> As noted previously, in two clinical studies in patients with advanced cancer and severe cachexia, LC oral administration (either 2 or 4 g for 4 weeks and 4 months, respectively<sup>15,42,48</sup>) failed to reduce blood levels of ROS, in spite of amelioration in fatigue symptoms and improved nutritional parameters (such as lean body mass and appetite).

#### ***L-carnitine and cancer-related fatigue***

The National Comprehensive Cancer Network (NCCN) defined the cancer-related fatigue (CRF) as "an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning."<sup>53</sup> Fatigue is a highly prevalent condition among cancer patients that severely affects patient's quality of life. Generally, around 50% to 100% of cancer patients experience fatigue. One of the important outcome of cancer related cachexia is fatigue.

Although, the underlying pathophysiology of CRF is unclear and very complex, an effective management of CRF can significantly reduce the cancer complications. Numerous pharmacological and non-pharmacological, exercise and psychosocial interventions have been used to reduce the burden of CRF. Among pharmacological modalities, several drugs, such as psychostimulants methylphenidate,<sup>54,55</sup> dexamphetamines<sup>56</sup> and modafinil<sup>57</sup> antidepressants,<sup>58-60</sup> corticosteroids,<sup>61,62</sup> donepezil<sup>63</sup> and guarana<sup>64</sup> have been studied. The most promising results were reported by methylphenidate, modafinil and guarana.<sup>65</sup>

LC supplementation is commonly used by cancer patients to treat CRF because patients with advanced cancer are at risk for LC deficiency due to decreased gastrointestinal intake and increased renal loss. Some chemotherapy drugs interfere with the carnitine network. Some data for a negative relationship between plasma LC and fatigue in children and adolescents with cancer have been published.<sup>23</sup> However, Hook et al failed to find evidence supporting a significant difference between LC levels and fatigue in a study of 58 patients between the ages of three and 18 years.<sup>66</sup> In a small, open-label trial including 50 patients with cancer who have not exhibited significant anemia or other conditions associated with asthenia, LC was administered in doses of 4 g per day for one week. This treatment increased plasma-free carnitine concentrations and significantly improved fatigue, which was assessed using the functional assessment of cancer therapy, fatigue, and quality of life questionnaire, as well as quality-of-life measures.<sup>67</sup>

Cruciani et al designed a phase III, randomized, doub-

le-blinded, placebo-controlled trial, in which 2 g per day of LC was administered orally for four weeks among eligible patients.<sup>68</sup> The primary endpoint was a change in average daily fatigue based on a baseline established using the brief fatigue inventory. LC supplementation resulted in a significant increase in the plasma LC, although no significant improvement was reported for fatigue, depression, or pain. A preliminary analysis of this study was published in 2004, which reported improvements in endpoints compared to baselines.<sup>69</sup>

A prospective, multi-centre, placebo-controlled, randomized, and double-blinded trial conducted by Kraf et al provided encouraging clinical data for the beneficial effects of LC on cancer.<sup>70</sup> In this study, 72 patients with advanced pancreatic cancer received either LC (4 g/day orally) or a placebo for 12 weeks. The results showed that body mass index, nutritional status (body cell mass and body fat), and quality-of-life parameters increased significantly in patients who received LC compared to the placebo group. There was an insignificant increase in overall survival, a decline in length of hospital stays, and decrease in fatigue among the LC-treated patients. Thus, LC may be an inexpensive and well-tolerated oral supplementation for patients with cancer.

Finally, in a recently published randomized study, the CRF ameliorating efficacy of the amino acid jelly, Inner Power®, which is a semi-solid, orally administered dietary supplement containing the coenzyme Q10 and LC, was assessed among breast cancer patients in Japan. During a 21-day follow up, the primary endpoint was the level of fatigue, which was measured using the brief fatigue inventory as well as changes from baseline were evaluated. The secondary endpoints, including global fatigue score, anxiety, depression, quality of life, and adverse events, were also assessed. Changes in the level of fatigue, global fatigue score, and current feelings of fatigue were significantly positive between the intervention and control groups, while changes in average feelings of fatigue were not significantly different between groups. Thus, this combination of supplements can control moderate to severe CRF in breast cancer patients.<sup>71</sup>

Taken together, according to controversy results, further future large and well-designed researches are needed to confirm the protective effects of LC on CRF.

Table 1 summarized the clinical studies regarding the possible effects of LC and its esters on cancer induced fatigue or cachexia syndrome.

#### ***Other possible nutritional strategies***

Recently, data from pilot and primarily studies proposed that specific branched-chain amino acids such as leucine, arginine, and glutamine may potentially be effective for attenuating muscle loss. They also have positive effects on cancer cachexia and can potentiate muscle anabolism.<sup>72</sup> However; no data exist to our knowledge comparing the efficacy of LC against that of amino acids or other possible nutritional modalities. Amino-acid supplementation has yet to be tested for efficacy or safety in clinical trials.

#### ***Conclusions and future perspectives***

Comprehensive assessments of both animal and clinical

studies of LC supplementation have shown that several protective mechanisms are involved in LC prevention of skeletal muscle loss in cancer conditions. Many non-human studies demonstrated that LC supplementation improved nitrogen balance in skeletal muscles, either because of increased protein synthesis or reduced protein degradation. Other proposed mechanisms include inhibition of apoptosis, inflammatory processes, oxidative stress, and amelioration of mitochondrial functions under pathologic conditions, such as cancer. However, there is insufficient evidence for the protective effects of LC supplementation on mitochondrial restoration during cancer, but several animal<sup>73-75</sup> and clinical studies of other pathologic conditions, such as traumatic spinal cord injury,<sup>76</sup> hemodialysis<sup>77</sup> and HIV<sup>78</sup> have confirmed these mechanisms. These results can be extrapolated to other pathologic conditions, such as cancer, and future studies should be conducted to verify that these results are similar in cancer condition. Despite the promising results from animal studies, the protective effects of LC on muscle loss from the majority of clinical studies were inconsistent and require further research.

It is worth mentioning that administration of different dietary regimens in control groups resulted in inconsistencies with respect to how the studies were designed. For instance, some dietary factors, such as food intake restriction and intake of LC and certain micronutrients (vitamin C, vitamin B6, and iron, which are required as co-factors for endogenous LC biosynthesis) may have some effects on the efficacy of LC supplementation and subsequently on the outcomes of the studies.

Diet macronutrients may effect plasma LC concentrations and urinary LC excretion in humans.<sup>79</sup> The rate of LC excretion increases after a high-protein diet and high-fat diet compared with a high carbohydrate diet and/or low-protein diet. In many of the published clinical studies, the composition of dietary regimens or the dietary macronutrient conditions are not clearly described. Further evaluation is needed of this topic in the form of clinical studies before conclusions can be drawn.

Recently, the large phase III study conducted by Mantovani et al provided encouraging results by demonstrating the efficacy of an LC in counteracting the clinical symptoms of cachexia.<sup>48</sup> Similarly, Gramignano et al confirmed the significant improvement of fatigue and quality of life as well as nutritional variables by LC administration.<sup>42</sup> However, some clinical trials failed to show any significant improvement of cachexia symptoms, probably due to the low dose or sample size limitation.<sup>69</sup>

In general, the number of clinical studies exploring the effect of LC supplementation on mechanisms involved in muscle wasting is rather small. The small sample size and different patient populations used across the studies comprising this review is another limitation. Therefore, the efficacy of LC supplementation as a supplement for anti-wasting therapy remains to be proven with a greater number of double-blinded, randomized, placebo-controlled trials. Irrespective of its efficacy, it is worth mentioning that none of the clinical studies examining LC supplementation reported any adverse effects even at very high dosages (e.g., 4 g per day, oral). Safety concerns with LC supplementation appear to be unfounded.

**Table 1.** Clinical studies regarding the effect of LC and its derivatives on cancer induced fatigue or cachexia syndrome.

Study	Design	Subjects and characteristics	Dose/route of administration	Treatment duration	Results
Breitkreutz R et al, 2000 <sup>50</sup>	double-blinded RCT <sup>†</sup>	28 cancer patients (10 M/4 W), aged 64.0±9.9 years	2 g/day LC orally	5 days	Decrease in the plasma glutamate, not significant increase in the relative glutamate uptake.
Graziano F et al, 2002 <sup>67</sup>	Open-labeled trial	50 cancer patients (30 M /20 W), aged 45-70 years	4 g/day LC orally	1 week	Amelioration in fatigue and the mean functional assessment of cancer therapy-fatigue score.
Gramignano G et al, 2006 <sup>42</sup>	RCT, unblended	12 cancer patients (2 M /10 W), aged 60±9 years	2 g/day LC orally	4 weeks	No change in serum-TNF $\alpha$ <sup>‡</sup> , IL-6 <sup>‡</sup> , and IL-1 $\beta$ <sup>‡</sup> . Fatigue symptom, nutritional variables, and levels of ROS <sup>§</sup> decreased. Glutathione peroxidase level increased.
Mantovoni G et al, 2008 <sup>15</sup>	RCT	125 cancer patients (74 M /51 W), aged 35–81 years	4 g/day LC orally	4 months	No change in serum-TNF $\alpha$ , IL-6, levels of ROS, improvements of nutritional variables and fatigue symptoms.
Cruciani RA et al, 2011 <sup>68</sup>	Double-blinded, placebo-controlled, RCT	376 cancer patients (157 M /219 W)	2 g/day LC orally	4 week	No significant change in fatigue and fatigue score.
Madeddu C et al, 2012 <sup>49</sup>	Phase III, RCT	Patients (17 M /12 W) (aged 18–85 years)	LC 4 g/day + celecoxib 300 mg/day ± megestrol acetate 320 mg/day orally	4 months	Improve in lean body mass, Physical performance and serum levels of IL-6, TNF- $\alpha$ and CRP <sup>¶</sup> , Drug combinations were safe and effective.
Kraft M et al, 2012 <sup>70</sup>	A randomized multicenter trial, RCT	72 patients suffering from advanced pancreatic cancer. (43 M /29 W)	Oral liquid formulation of LC (4 g/d)	12 weeks	Improvement in body cell mass, body fat and nutritional status and quality of life. No significant benefit in reduction of hospital stay, fatigue and survival.
Iwase S et al, 2016 <sup>71</sup>	RCT	59 cancer patients aged 29-70 years	Branched-chain amino (2500 mg), coenzyme Q10 (30 mg), and LC (50 mg) orally	21 days	Improve in level of fatigue, global fatigue score, and current feeling.

M: men; W: women.

<sup>†</sup>Randomized Controlled Trial (RCT) is a study in which people are allocated randomly to receive one of several clinical interventions.

<sup>‡</sup>Tumor Necrosis Factor (TNF) and interleukins (IL), are cell signalling protein (cytokine) involved in systemic inflammation and acute phase reaction.

<sup>§</sup>Reactive Oxygen Species (ROS) are chemically reactive chemical species containing oxygen.

<sup>¶</sup>C - reactive protein (CRP) is a blood test marker for inflammation in the body.

**AUTHOR DISCLOSURES**

No author has any potential conflict of interest.

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