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Review Article

Biomedical role of L-carnitine in several organ systems, cellular tissues, and COVID-19

Papel biomédico da L-carnitina em vários sistemas de órgãos, tecidos celulares e COVID-19

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Abstract

Carnitine is a conditionally necessary vitamin that aids in energy creation and fatty acid metabolism. Its bioavailability is higher in vegetarians than in meat-eaters. Deficits in carnitine transporters occur because of genetic mutations or in conjunction with other illnesses. Carnitine shortage can arise in health issues and diseases—including hypoglycaemia, heart disease, starvation, cirrhosis, and ageing—because of abnormalities in carnitine control. The physiologically active form of L-carnitine supports immunological function in diabetic patients. Carnitine has been demonstrated to be effective in the treatment of Alzheimer's disease, several painful neuropathies, and other conditions. It has been used as a dietary supplement for the treatment of heart disease, and it also aids in the treatment of obesity and reduces blood glucose levels. Therefore, L-carnitine shows the potential to eliminate the influences of fatigue in COVID-19, and its consumption is recommended in future clinical trials to estimate its efficacy and safety. This review focused on carnitine and its effect on tissues, covering the biosynthesis, metabolism, bioavailability, biological actions, and its effects on various body systems and COVID-19.

Keywords: L-carnitine, diabetes mellitus, cardiovascular disease, obesity.

Resumo

A carnitina é uma vitamina condicionalmente necessária que auxilia na geração de energia e no metabolismo de ácidos graxos. Sua biodisponibilidade é maior em vegetarianos do que em carnívoros. Déficits nos transportadores de carnitina ocorrem devido a mutações genéticas ou em conjunto com outras doenças. A escassez de carnitina pode surgir em problemas de saúde e doenças – incluindo hipoglicemia, doenças cardíacas, fome, cirrose e envelhecimento – devido a anormalidades no controle da carnitina. A forma fisiologicamente ativa da L-carnitina suporta a função imunológica em pacientes diabéticos. A carnitina demonstrou ser eficaz no tratamento da doença de Alzheimer, várias neuropatias dolorosas e outras condições. Tem sido utilizado como suplemento dietético para o tratamento de doenças cardíacas, também auxilia no tratamento da obesidade e reduz os níveis de glicose no sangue. Portanto, a L-carnitina mostra potencial para eliminar as influências da fadiga na COVID-19 e seu consumo é recomendado em futuros ensaios clínicos para estimar sua eficácia e segurança. Esta revisão enfocou a carnitina e seu efeito nos tecidos, abrangendo a biossíntese, metabolismo, biodisponibilidade, ações biológicas e seus efeitos em vários sistemas corporais e COVID-19.

Palavras-chave: L-carnitina, diabetes mellitus, doença cardiovascular, obesidade.

1. Introduction

L-Carnitine (LC) is a quaternary ammonium compound. It is considered and its two derivatives (acetyl-L-carnitine and propionyl-L-carnitine) essential amino acid lysine which plays important role in cellular energy metabolism, as shown in Figure 1. In 1905, it was discovered in beef ('carnus' in Latin). Carnitine's L-isomer is the only isomer that is physiologically active (Rebouche, 2006). LC, which resembles a vitamin in mealworms, was given the moniker vitamin BT. Humans and other higher animals can generate LC; thus, vitamin BT is a misnomer. However, in rare cases, an individual's demand for LC may make it an essential vitamin (Seim et al., 2001; De Grandis and Minardi, 2002).

The carnitine molecule has a gamma trimethyl amino beta-hydroxybutyric acid structure with D and L forms; D-carnitine inhibits LC's function. Only the L-form, which is biologically active, is generated endogenously in tissues (such as the brain, kidneys, and liver) through conversion from amino acids, including lysine and methionine; this process accounts for 25% of the body's LC. The remaining 75% is derived from food sources (Çitil, 2002; Hoppel, 2003).

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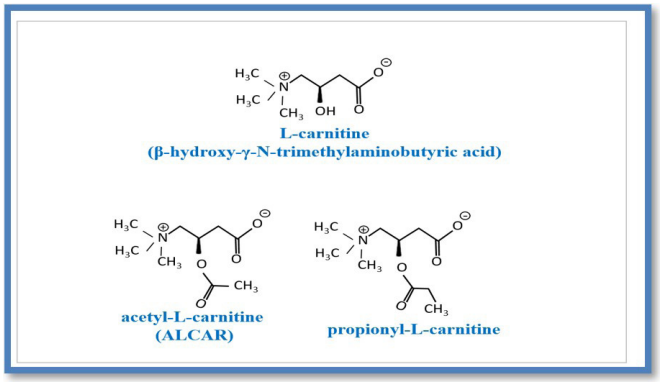

Figure 1. L-Carnitine chemical structures and its two derivatives (Durazzo et al., 2020).

It is typically consumed in food and stored in the skeletal muscle (Rebouche, 2004). The fundamental function of this key metabolite is to ensure the movement of fatty acids from the cytoplasm through the mitochondria so that they can be used for mitochondrial oxidation (Seline and Johein, 2007). LC assists in the beta-oxidation of fatty acids, which serve as energy sources in the form of acylcarnitine. Second, it protects mitochondria from the damaging effects of free coenzyme A (CoA) generated during the digestion of short- and medium-chain fatty acids (Calabrese et al., 2012).

LC has been shown to improve physical performance in patients with certain illnesses, including advanced cancer (Bloomer et al., 2013), fatigue (Gramignano et al., 2006), metabolic syndrome, and cardiovascular disease (CVD) (Delaney et al., 2013).

Long-term supplementation with LC is likely safe at doses of 2 g/day, but it may lead to indigestion, vomiting, diarrhoea, nausea, or fishy body odour at doses of 3 g/day (Rebouche, 1999).

2. Metabolism, Bioavailability, and Biosynthesis

Cellular metabolism is a complex biochemical process that is necessary for organisms to maintain life. It mainly occurs in the mitochondria, which work to convert food into energy by oxidising fatty acids. Therefore, a disruption in mitochondrial function leads to deficient energy production, an accumulation of fatty acids in the cell, and an increase in reactive oxygen species (Virmani and Cirulli, 2022). LC is an essential component and plays a role in mitochondrial processes, ATP energy production, and fatty acid metabolism. It is also involved in controlling gluconeogenesis, ketogenesis, cellular detoxification, and stabilising cell membranes (Wang et al., 2021 a). In the mitochondria, the transport of long-chain fatty acids for energy production in peripheral tissues is dependent on LC (Center et al., 2000). LC is necessary for the oxidation and transport of fatty acids through the inner mitochondrial membrane (Broad et al., 2011; Pandareesh and Anand, 2013).

Carnitine is necessary for the esterification of long fatty acid chains in the mitochondria, which provides energy through beta-oxidation via a series of reactions that convert fatty acids into acetyl-CoA. In the cytoplasm, fatty acids are converted to acyl-CoA, and LC stimulates the transfer of an acyl group from the cytoplasm to the mitochondria by binding to the carnitine shuttling system on the mitochondrial membrane. L-Carnitine palmitoyltransferase-1 (CPT I), which is located on the outer surface of the mitochondria, releases CoA to form an acylcarnitine. Acylcarnitine is transported across the mitochondrial membrane and into the mitochondria matrix via L-carnitine/acyl-L-carnitine translocase (CAC), as shown in Figure 2. In the mitochondrial matrix, the acyl group of carnitine is dissociated and linked back to coenzyme A by LC palmitoyltransferase-2 (CPT II), which is present in the inner mitochondrial membrane, to import long-chain FA into the mitochondria for beta-oxidation, which provides energy for cells (Wang et al., 2021b).

Carnitine homeostasis is maintained in healthy persons by dietary carnitine absorption, renal carnitine reabsorption, and endogenous LC production. Cell membrane transporters distribute carnitine between the extracellular compartment and the tissues, maintaining the concentration gradient between them. Humans can obtain carnitine from red meat, chicken, some types of fish, and dairy products; thus, the intake of carnitine for vegetarians is very low because their diets lack foods rich in carnitine sources. The daily dietary intake of carnitine should range between 1 and 15 µmol/kg of body weight. Carnitine from food is absorbed by the epithelial cells lining the small intestine, where it is transported by simple diffusion into the blood circulation. The kidneys reabsorb carnitine through active transport by transporters present in the brush border membranes of the renal tubular cells, and when the dietary intake of carnitine decreases, its reabsorption by the kidneys increases (Rebouche, 2004; Kraemer et al., 2008).

The amino acids lysine and methionine can be converted to LC in humans via a multi-step process involving numerous cells. Lysine methyltransferases, which are utilised as methyl donors, are made from the amino acid methionine and methylate protein-bound lysine to generate 6-N-trimethyl lysine, which is essential for carnitine synthesis. The hydroxylation of 6-N-trimethyl lysine yields 3-hydroxy-6-N-trimethyl lysine, which is separated into 4-trimethylaminobutyraldehyde and

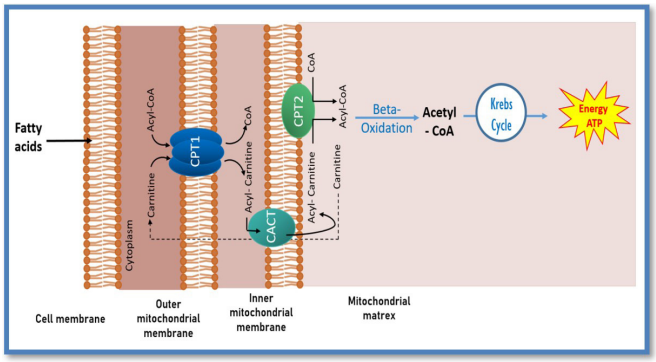

Figure 2. The role of L-carnitine in fatty acid metabolism in mitochondria (Wang et al., 2021b).

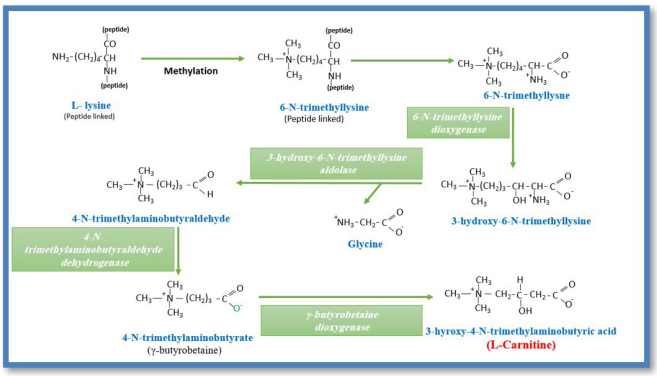

Figure 3. L-Carnitine biosynthesis takes place in six steps, interspersed with four important enzymes (green box) (Furusawa et al., 2008).

glycine; subsequently, trimethylaminobutyraldehyde is dehydrogenated to form 4-N-trimethylaminobutyrate (γ-butyrobetaine), and this compound produces LC (3-hyroxy-4-N-trimethylaminobutyric acid or β-hydroxy-γ-N-trimethylaminobutyric acid). Endogenous LC production is mediated by four enzymes, as shown in Figure 3. Except for butyrobetaine hydroxylase, which is not found in the cardiac or skeletal muscle, all four enzymes are widely distributed. However, these enzymes are abundant in the liver, testes, and kidneys in humans (Rebouche, 2014).

L-Carnitine is produced in the liver and transported to the cardiac and skeletal muscle, where it is required for fatty acid oxidation, but it cannot be produced in vegetarians; it was synthesised at a rate of 1.2 mol/kg of body weight/day (i.e., persons who receive relatively little dietary carnitine) (Evans and Fornasini, 2003). The quantity of methylation on peptide-linked lysine and the average protein rotation controls the pace of LC production. Increased lysine in the diet can boost endogenous LC synthesis; by contrast, LC intake does not affect the rate of endogenous synthesis (Rebouche, 2014).

3. Biological Activities

3.1. L-Carnitine and diabetes mellitus

LC is an essential component of the human body that promotes the proper function of the heart and muscular system. It also aids in the appropriate use of glucose by the cell, improving glucose metabolism in patients with diabetes and reducing problems such as tiredness, sleeplessness, and mental activity (Karalis et al., 2020).

Clinical supplementary LC might help people with poor glucose metabolism improve their glucose tolerance. LC increases the oxidation of fatty acids, which can contribute to insulin resistance in the skeletal muscle; therefore, it may be advantageous to these patients (Ringseis et al., 2013). Supplemental LC was found to lower insulin resistance compared with placebo in a meta-analysis including patients with weakened fasting glucose, type 2 diabetes (T2D), and non-alcoholic steatohepatitis (Xu et al., 2017). A meta-analysis of four randomised, placebo-controlled studies demonstrated a decrease in fasting plasma glucose concentration but no change in glycated haemoglobin concentration in patients with T2D mellitus treated with acetyl-L-carnitine (ALCAR) (Vidal-Casariego et al., 2013). Supplementing with (acyl)-L-carnitine may lower fasting blood glucose and glycated haemoglobin concentrations but not insulin resistance (Asadi et al., 2020). The impact of ALCAR was studied in 229 patients with diabetes, hypertension, and dyslipidaemia in a randomised, controlled experiment. The results showed that supplementing with ALCAR (1 g/day for 6 months) had no influence on blood pressure, markers of glucose homeostasis, or blood

lipid profile (Parvanova et al., 2018). However, therapy with LC has proven to be beneficial for the control of diabetes, insulin resistance, high blood pressure, and dyslipidaemia in prior investigations (Zhang et al., 2014). In patients with T2D, LC supplementation resulted in a considerable reduction in lipid profile levels. According to the National Cholesterol Education Program (NCEP, 2001), all risk factors for diabetic patients should be decreased to lower patients' total CVD risk.

About half of people with diabetes mellitus have peripheral nerve dysfunction, and about a third of those with diabetes have persistent neuropathic pain (Tesfaye and Selvarajah, 2012). As diabetic peripheral neuropathy progresses, it can cause recurring foot sores and infections, which can require amputation (Dy et al., 2017).

Rolim et al. (2019) and Sima et al. (2005) identified some studies that examined the effects of oral ALCAR supplementation in diabetic patients. ALCAR was shown to decrease the degree of pain and improve clinical symptoms in patients with diabetic peripheral neuropathy, as evaluated by a visual analogue scale, according to low-quality data (Li et al., 2016).

3.2. L-Carnitine and cardiovascular disease

LC functions as a vitamin in the body's metabolic activities. In a range of illnesses, including CVD, diabetes, and dyslipidaemia, high levels of LC have been shown to be beneficial (Ferrari et al., 2004).

Because it is unable to produce carnitine, human skeletal and cardiac muscle absorbs relatively high levels of it from the plasma. In carnitine-acylcarnitine carrier (CAC) deficiency, the heart is one of the most damaged organs**;** CAC promotes the import of fatty acyl moieties into the mitochondria, where they are oxidised via the beta-oxidation pathway by increasing carnitine/acylcarnitine exchange. The heart obtains most of its energy from this source, so CAC deficiency causes cardiomyopathy, cardiac arrhythmia, cardiac insufficiency, and respiratory distress (Palmieri, 2008). Heart failure has also been linked to a lack of carnitine (Cave et al., 2008).

The mechanism or mechanisms behind LC's actions in cardiovascular disorders remain unknown. The effects of long-term LC administration on the inflammatory process associated with arterial hypertension were identified in a rat model (Miguel-Carrasco et al., 2008).

LC, the physiologically active dietary carnitine (3-hydroxy-4-N-trimethylaminobutyric acid), is a promising alternative medication for secondary heart disease prevention. The carnitine/organic cation transporter-2 (OCTN2) allows cardiac muscle cells to receive LC from outside sources. OCTN acts as a carnitine transporter in the heart, kidney, liver, pancreas, intestine, brain, placenta, trachea, lung, and thyroid. The carnitine-acylcarnitine carrier (CAC) is a protein that allows cardiac mitochondria to oxidize fatty acyl, which is the main source of energy for the heart muscle, and deficits in LC or its transporter CAC can cause heart disease (Flanagan et al., 2010).

LC supplementation can benefit patients with heart disease because it assists in the return of cardiac energy stores (Flanagan et al., 2010). LC supplementation for 12 months in patients with chronic heart disease patients was demonstrated to reduce chronic heart diseases and mortality. As an oral treatment, it was demonstrated to minimise myocardial damage while enhancing glucose metabolism and reducing the toxicity of elevated free fatty acid levels (Xue et al., 2007).

Several studies have found that administering LC right after a heart attack might help to decrease ischemia-induced cardiac muscle damage. Taking oral LC in addition to normal pharmacological therapy for a year decreased mortality and angina episodes considerably (Davini et al., 1992). Another controlled study including 96 patients found that intravenous LC treatment reduced levels of creatine kinase-MB and troponin-I, two markers of myocardial injury, after myocardial infarction (MI) (Xue et al., 2007). However, not all clinical research has indicated that supplementing with LC after a heart attack is beneficial. In a randomised trial involving 60 people who had an acute MI, no differences in heart function were found between those who received intravenous LC and those who received a placebo (Iyer et al., 1999). Another randomised study found that LC therapy did not affect the incidence of heart failure or death 6 months after MI (Tarantini et al., 2006).

In individuals who had acute MI, LC treatment reduced the risk of death, ventricular arrhythmias, and angina. The rupture of an atherosclerotic plaque in a coronary artery obstructs the blood flow to the heart muscle, causing injury or damage to the heart muscle and MI (DiNicolantonio et al., 2013). Because oral LC supplements are unlikely to be absorbed, procedures that mix intravenous and oral administration are equal to those that employ only oral administration (Evans and Fornasini, 2003).

Oral LC supplementation for a long time has been shown to decrease metabolic syndrome and CVD risk factors (Wong et al., 2016). According to Wu (2016), LC can improve lipid profiles and reduce diabetes and heart disease while also improving clinical symptoms in patients with diabetes and heart failure.

When cardiomyocytes experience cardiac failure, they have problems converting substrates into energy; LC levels in the blood are reduced after coronary artery graft surgery, and oxidative stress is increased. LC supplementation in these individuals has shown benefits in the clinical setting (Silva et al., 2017).

Wang et al. (2018) mentioned that LC is an endogenous cofactor and may be associated with an increase in mitochondrial oxidation and production of cardiac energy. It increases fatty acid transport across the mitochondrial matrix, lowering oxidative stress, inflammation, and myocyte necrosis while also offering cardioprotective benefits. LC also adjusts calcium influx, intracellular enzyme release, and membrane phospholipid content, all of which contribute to cellular homeostasis. As a result, dietary and intravenous exogenous carnitine supplementation are efficient strategies for reducing ventricular dysfunction, ischemia-reperfusion damage, cardiac arrhythmia, and toxic myocardial injury are all reduced, all of which are prevalent symptoms of CVD. Hypertension, hyperlipidemia, diabetic ketoacidosis, hyperglycemia, hyperglycaemia insulin-dependent diabetes mellitus, insulin resistance, obesity,

and other variables are all improved by LC. Individuals with acute and chronic heart failure in various age groups, including infants, juveniles, young adults, adults, and older adults, can benefit from LC.

3.3. L-Carnitine and lipid profile

LC boosts fat oxidation and glycogen sparing during exercise, which increases physical performance (Johri et al., 2014). It has a variety of physiological functions, including antioxidant preservation and increased nitric oxide synthesis (Bacurau et al., 2003). Moreover, LC improves energy generation from fatty acid oxidation (Gulcin, 2006), particularly from adipose tissue triglycerides (TAG), and optimises the utilisation of adenosine triphosphate (ATP) as a fuel substrate during exercise (Sahlin et al., 2008). LC also regulates the mitochondrial ratio and activates carnitine acyltransferases (CAT), which transport fatty acids across the mitochondrial membrane (Karlic and Lohninger, 2004).

Carnitine may influence triglycerides as well as total cholesterol and its fractions. In obese and insulin-resistant ponies, 14 weeks of carnitine administration reduced blood lipid profile levels (Schmengler et al., 2013). Furthermore, Coleman and Lee (2004) suggested that with elevated physiological carnitine levels in the liver, very-low-density lipoprotein (LDL), triglyceride, and cholesterol secretion rates were lower. As a result, reduced LDL production is predicted to raise plasma high-density lipoprotein (HDL) levels. Athletes have long been interested in using carnitine to improve physical performance by enhancing ATP production, with several types of carnitine being employed. Previous research suggested that muscle carnitine is reallocated in the muscle after intense physical exercise (Muller et al., 2002).

LC is an unbound, water-soluble amine, allowing for an increase in fatty acid metabolism (Hoppel, 2003). Furthermore, LC may alter glucose catabolism by transporting acetate from the mitochondria to the cytoplasm, lowering the acetyl CoA/CoA ratio in the mitochondria and enhancing pyruvate dehydrogenase activity. Other studies have found that LC may raise fasting TAG in patients with diabetes (Rahbar et al., 2005).

Therefore, pharmaceutical agents that can correct blood lipid abnormalities, particularly in people with T2D, are critical. Accordingly, the impact of nutraceuticals on cardiovascular risk factors is a currently a hot research topic (Ward et al., 2017). The pharmacological benefits of LC as an additional treatment for dyslipidaemia, notably in individuals with T2D, have been described in several investigations (Rahbar et al., 2005).

LC is a vitamin-like molecule made up of lysine and methionine that is necessary for the fatty acid oxidation in the mitochondria and the protection of cell membranes from free radical damage (Peivandi et al., 2010). In patients with chronic renal disease, intake of LC supplements led to a decrease in the level of cholesterol and triglycerides, and an increase in haemoglobin and HDL (Naini et al., 2012).

In a meta-analysis of patients with cardiovascular risk aiming to evaluate the effect of LC intake on lipid profile, lipid level improvement was demonstrated at doses of over 1500 mg/day (Asadi et al., 2020). The meta-analysis also showed a decrease in the level of total cholesterol and TAG in the blood of patients with chronic hepatitis C who took LC supplements at a dose of 2000 mg/day for approximately 24 weeks, and no changes in the levels of HDL or LDL were observed (Abbasnezhad et al., 2020).

3.4. L-Carnitine and weight loss

Obesity is a worldwide epidemic that can lead to dyslipidaemia (Fried et al., 2008), diabetes (Pagotto et al., 2008), fatty liver (Marović, 2008), and heart problems (Artham et al., 2008). Individuals often use pharmacotherapy to help them lose weight. Carnitine is one of the medications that claim to help people with weight loss.

Obesity is a severe health issue that has become increasingly linked to elevated rates of mortality and morbidity throughout the world. Weight reduction is becoming more popular as weight control becomes increasingly challenging in the modern environment. Anti-obesity medicines do not have the same negative side effects as invasive operations, and thus they are more popular than alternative choices, such as physical activity. Carnitine has been used to treat heart disease (Shang et al., 2014), end-stage renal disease (Chen et al., 2014), dialysis-related hypertension (Lynch et al., 2008), persistent depressive disorder, and fatty liver disease (Kriston et al., 2014). However, the data on carnitine's anti-obesity properties are currently equivocal. In one study, weight reduction was assessed using two variables: the individual's weight and their body mass index (BMI). Only seven participants had suitable data for quantitative examination. This study had good methodological quality, demonstrated that LC had a positive influence on weight and BMI, and showed that LC could help people with chronic illnesses, including diabetes and obesity, lose weight (Pooyandjoo et al., 2016).

LC, which is important for lipid catabolism and energy generation, is also important for muscle fuel metabolism during exercise and regulating muscle fuel metabolism (Kim et al., 2015). Along with the body's requirement for LC during high-intensity exercise, this suggests that LC ingestion enhances fat oxidation during extended exercise, preserves glycogen stores, and delays tiredness onset (Kraemer et al., 2008).

With its two impacts on glucose and lipid metabolism, LC may aid metabolic illnesses such as T2D and hypertriglyceridemia. LC is a well-known weight-loss and fat-burning substance, and according to a meta-analysis, supplementing with LC lowered body weight, BMI, and fat mass (Pooyandjoo et al., 2016; Talenezhad et al., 2020). Supplementing with LC lowers blood pressure by minimising interactions with the nitric oxide system and insulin resistance (Rajasekar et al., 2007).

According to Askarpour et al. (2019), LC supplementation at taken 2 g/day lowers diastolic blood pressure (DBP) without changing systolic blood pressure (SBP). By enhancing carbohydrate oxidation and lowering fatty acid oxidation, LC supplementation at a dose of 2-3 g/day was linked to improved fasting blood sugar (FBS) and insulin resistance (Vidal-Casariego et al., 2013). LC plays a key role

in fatty acid beta-oxidation and lowers the availability of free fatty acids for triglyceride production. In a study conducted by Malaguarnera et al. (2009), LC lowered TAG concentrations while increasing HDLc concentrations.

The intake of LC in patients who are obese and overweight leads to a decrease in body weight and BMI, suggesting that it has an anti-obesity effect (Askarpour et al., 2020).

3.5. L-Carnitine and liver and kidney disease

The most prevalent dose-limiting adverse effects of cisplatin-induced chemotherapy are hepatic and renal damage (Neamatallah et al., 2018). Using LC to reduce the possible negative effects of cisplatin is beneficial during chemotherapy. Elevated liver enzyme activity is recognised as an indication of cellular infiltration and loss of function of hepatocytes because these enzymes are discharged into the blood when the hepatocyte plasma membrane is disrupted (Jia et al., 2018; Farid et al., 2021; Fadl et al., 2020). It was shown that cisplatin-induced hepatotoxicity was accompanied by a considerable change in blood liver enzymes. Cisplatin is absorbed by and deposited in the liver cells, producing damage and an elevation in liver enzyme activity (Mohamed and Badawy, 2019). Furthermore, cisplatin raises creatinine and urea levels (Sadeghi et al., 2020) and indicates cisplatin-induced nephrotoxicity. By contrast, Cayir et al. (2009) ascribed cisplatin hepatotoxicity and nephrotoxicity to free radical formation in kidney and liver cellular, which causes cellular damage.

Furthermore, LC is a naturally occurring substance that is required to generate ATP (Tunez et al., 2007). As a result, it contains antioxidant qualities and protects numerous tissues from oxidative stress (Cayir et al., 2009). In a rat model, LC lowered liver enzyme activity, oxidative stress, and thioacetamide and tilmicosin-induced damage (Aboubakr et al., 2020). In rats with acute renal failure, LC increased the antioxidant enzyme activity in kidney tissues (Aydogdu et al., 2006). Therefore, LC's ability to protect numerous tissues may be due to its antioxidant effect, resulting in membrane permeability protection (Augustyniak and Skrzydlewska, 2009). LC protects against mitochondrial toxic chemicals and oxidative stress (Barhwal et al., 2007). It also enables beta-oxidation, which reduces the detrimental effects of free fatty acids (Furuno et al., 2001).

People with acute or chronic liver illness can exhibit hepatic encephalopathy, which refers to a variety of neuropsychiatric signs and symptoms. There may be no indications of subclinical hepatic encephalopathy other than aberrant conduct on psychometric tests or vague symptoms. Disorientation, evident personality changes, inappropriate conduct, somnolence, stupor, confusion, and coma are among the symptoms of overt hepatic encephalopathy. The liver's failure to metabolise neurotoxic chemicals, such as ammonia, is assumed to be the source of mental changes (Wijdicks, 2016).

Although excess valproic acid does not cause toxidrome, it can deplete hepatic LC reserves, making mitochondrial transport via the carnitine shuttle more difficult. Despite a lack of evidence, LC has been recommended as a feasible treatment for restoring mitochondrial function, minimising toxic metabolite formation, and counteracting or reversing the toxic effects of valproic acid. A comprehensive analysis identified only eight occurrences of acute valproic acid exposure in adults and children, as well as one study that published safety data from 674 people. Because LC has low oral bioavailability, intravenous therapy was recommended; in addition, most overdose patients were given activated charcoal, rendering oral LC ineffective. According to data from these cases and toxicological sources, the most common loading dose was 100 mg/kg, with another dose of 50 mg/kg, to address ongoing or delayed toxicity induced by valproic acid absorption. Despite the dearth of data and the likelihood of publication bias, the authors concluded that LC treatment was appropriate for individuals with acute overdose and low levels of consciousness (Perrott et al., 2010). In addition, a case report described the use of LC to treat PEG-asparaginase-induced hepatotoxicity in a patient with acute lymphoblastic leukaemia (Alshiekh-Nasany and Douer, 2016).

Yang et al. (2014) conducted a systematic review and meta-analysis to assess prior findings showing that LC had favourable effects on haemoglobin and erythropoietin dosage in patients undergoing maintenance haemodialysis. Although LC supplementation reduced LDL cholesterol and C-reactive protein (CRP), it had no effect on other lipid markers, haemoglobin, haematocrit, albumin, or the erythropoietin dosage required. The drop in LDL cholesterol was assumed to be insignificant in clinical terms. There were no known negative consequences (Chen et al., 2014). Because of a lack of evidence, the Renal Illness Improving Global Outcomes (KDIGO) clinical practice guidelines for anaemia in chronic renal disease do not advocate LC as an adjuvant treatment (KDIGO, 2012).

4. Physical Health

4.1. Physical performance

The importance of LC's function in energy metabolism has sparked interest in its potential to boost athletic performance. LC supplementation can be used for acute (2-4 g/day taken one hour before an exercise session) or in the short-term (for 2 to 3 weeks). According to several small studies, it can help with energy generation, cardio-respiratory fitness, and endurance capacity during physical activity (Fielding et al., 2018).

Because of its function in converting fat into energy, LC is a popular substance among athletes as a potential ergogenic aid (Kim et al., 2015). Propionyl-L-Carnitine (1 g/day or 3 g/day) did not increase aerobic or anaerobic exercise performance in 32 healthy people in an 8-week study (Smith et al., 2008). In a study examining the effects of LC supplementation on plasma and skeletal muscle carnitine concentrations and physical performance in 16 vegetarian and 8 omnivorous male volunteers, the plasma carnitine levels in vegetarians were 10% lower at baseline than those of omnivores. However, the carnitine levels in skeletal muscle phosphocreatine, ATP, glycogen,

and lactate were equal in vegetarians and omnivores, as were the measures of physical performance after exercise. Although LC treatment raised plasma carnitine levels in vegetarians above the levels reported in omnivores, no differences in energy metabolism or physical performance were observed between the two groups (Novakova et al., 2016). The skeletal muscle stores more than 95 per cent of the body's total carnitine and is involved in key metabolic processes, such as ATP synthesis (Stephens et al., 2007; Kim et al., 2015).

4.2. Frailty

Frailty is a serious age-related health problem marked by a considerable decrease in physiological reserves and a greater sensitivity to shock. Its phenotype (from pre-frailty to frailty) is a major predictor of severe unfavourable health problems, such as cardiovascular illnesses (Veronese et al., 2017), depression (Feng et al., 2014), hospitalisation, loss of fundamental daily activities, falls, fractures, and early death (Vermeiren et al., 2016). Frailty is more frequent in older adults because of the steady decline in their functional ability and the increase in functional dependency that occurs as people age (Siriwardhana et al., 2018). Furthermore, being female, single marital status, a lack of social support, a greater prevalence of comorbidities, disability, and functional restriction have all been identified as important risk factors for the emergence of frailty (Manfredi et al., 2019).

Frailty is a condition that affects older populations and is marked by a deterioration in function and a loss of independence in performing everyday tasks. Unintentional weight loss, fatigue, weakness, sluggishness, and physical inactivity are indications of frailty (Fried et al., 2004). Early stages of frailty are thought to be responsive to therapies that might prevent negative outcomes, such as increased hospitalisation and premature mortality (Vermeiren et al., 2016). One study investigated the theory that carnitine deficit leads to frailty by causing mitochondrial malfunction (Crentsil, 2010). The results of study on 50 older adult showed that participants who received LC supplementation exhibited a lower frailty index score and improved strength in a hand grip test, whereas those given a placebo did not (Badrasawi et al., 2016).

4.3. Skeletal and muscle weakness

Skeletal and muscle mass loss is linked to a loss of muscular strength and occurs as people age (Dhillon and Hasni, 2017) as well as in a variety of clinical diseases (Ebadi and Montano-Loza, 2019). A low proportion of protein synthesis and degradation leads to skeletal muscle atrophy; according to a preclinical study, LC supplementation may help increase this proportion (Ringseis et al., 2013). In a randomised controlled experiment including 28 older women, LC supplementation had no impact on serum pro-inflammatory cytokine concentrations, body mass and composition, or measures of skeletal muscle strength (Sawicka et al., 2018). The presence of a defect in liver function in patients with cirrhosis led to weakness and loss of skeletal muscle mass; this study was the first to show the protective effect of LC supplementation on the muscles. In a retrospective analysis of patients with cirrhosis, those who received LC had lower rates of skeletal muscle loss for at least 6 months compared with those who did not (Ohara et al., 2018).

4.4. Muscle cramps

Muscle cramps are painful involuntary skeletal muscle contractions. LC supplementation at levels of 0.9 to 1.2 g/day for 8 weeks was found to be effective in patients with cirrhosis in two uncontrolled studies (Nakanishi et al., 2015; Hiraoka et al. 2019), which found that LC supplementation was safe and could be used to reduce cramp frequency. However, supplemental LC has not yet been proven to be effective in reducing muscular cramps in cirrhotic individuals. A study of 69 patients with diabetes revealed that those who took LC once per day for four months had lower blood sugar levels, fewer muscle cramps, and a higher quality of life than those who took a placebo (Imbe et al., 2018). By contrast, there is currently no evidence that supplementary LC can prevent muscular cramps in individuals receiving haemodialysis (Lynch et al., 2008). To determine whether LC can assist with cramping, researchers will need to conduct well-designed experiments.

Patients with ongoing symptoms of painful, involuntary contractions of skeletal muscles at rest or waking them up at least three times in the previous month were included in a prospective uncontrolled, nonrandomised study evaluating the effects of LC on reducing muscle cramps in patients with cirrhosis. Participants were given LC for 8 weeks and reported decreased cramping, and no negative consequences were observed (Nakanishi et al., 2015).

5. L-Carnitine and Cellular Injury

The regulation of cell proliferation and differentiation is dependent on cellular metabolic activity, particularly mitochondrial metabolism. When applying engineering methods to drive tissue formation and repair, metabolism may be a significant component to consider. Carnitine and its derivative, acetylcarnitine, are tiny metabolites that influence the activity of multiple mitochondrial metabolic pathways. Adult stem cells were employed as a platform in both monolayer and 3D hydrogel culture systems to investigate the impact of these two small compounds on mesenchymal tissue engineering. The authors examined the effects of these two small compounds on adult stem cell differentiation, as well as gene expression, cell proliferation, and extracellular matrix deposition. In both culture systems, the compounds inhibited adipogenesis while stimulating osteogenesis and chondrogenesis. According to the findings of our previous study, carnitine and acetylcarnitine may impact the differentiation rate of adult stem cells by influencing mitochondrial metabolism. The action of these two compounds suggests that such metabolites may be used in tissue-engineering systems to improve cell differentiation and tissue formation (Lu et al., 2015).

The effects of LC (300 mg/kg/day) administered intraperitoneally to rats fed rations containing various proportions of fish oil for 30 days on plasma LC, lipid

hydroperoxide (LPO), triglyceride, cholesterol, body weight, plasma-tissue antioxidant enzymes (superoxide dismutase, carnitine acyltransferases), and glutathione levels were examined; LC modulated the plasma lipid profile and increased tissue antioxidant (Yavuz and Kurtoğlu, 2014).

LC plays an important role in intracellular energy metabolism in two ways. First, it participates in beta-oxidation by transporting long-chain fatty acids (12 to 20 carbon atoms) to mitochondria, providing an energy source in the form of acylcarnitine. Second, it reduces the toxicity of free CoA, which is produced when short-chain (4-6 carbon atoms) and medium-chain (6-12 carbon atoms) fatty acids are digested in the mitochondria (Calabrese et al., 2012).

LC is a naturally occurring molecule that aids long-chain fatty acid entrance into cellular mitochondria, providing a substrate for oxidation and subsequent energy generation. The structure of LC improves and preserves cognitive performance and contributes to improved cognitive ageing over time, and multiple controlled human clinical trials using LC have provided evidence that this substance can improve cognitive function. Furthermore, because LC is a key cofactor in mammalian mitochondrial energy metabolism, it was hypothesised that acute LC treatment of human tissue cultures would result in observable improvements in mitochondrial function. LC hydrochloride was given to cultures of SH-SY-5Y human neuroblastoma and 1321N1 human astrocytoma cells cultured in 96-well cell culture plates. When human neuroblastoma or human astrocytoma cells were exposed to 100 nM (20 µg LC hydrochloride/L) to 100 µM (20 mg LC hydrochloride/L) concentrations of LC hydrochloride, significant increases in mitochondrial function were observed in comparison with unexposed cells, whereas no significant positive effects were observed at lower or higher concentrations of LC hydrochloride (Geier and Geier, 2013).

6. L-Carnitine's Antioxidant and Anti-Inflammatory Effects

Oxidation is a process that occurs in the cells of the body. This process results in reactive oxygen species (ROS) and antioxidants; the body is normally able to maintain a balance between ROS and antioxidants, but an imbalance leads to oxidative stress. When ROS production is increased, it oxidises biomolecules or modifies proteins and activates transcription factors and pro-inflammatory genes, causing inflammation. Inflammation causes the body's immune cells to release cytokines and chemokines to recruit other immune cells to the site of oxidative stress (Chatterjee, 2016). In addition, inflammation is the immune system's response to infection and injury. LC plays an active role in the work of the immune system by increasing antioxidant activity and reducing oxidative stress and inflammation (Bellamine et al., 2021).

Previous studies have demonstrated that LC has an effective role as an antioxidant and anti-inflammatory, preventing the accumulation of the end-products of lipid peroxidation; when patients with renal diseases were given a carnitine supplement for 8 weeks at a dose of 20 mg/kg body weight, a decrease in biomarkers of oxidative stress was observed (Fatouros et al., 2010).

Administration of LC reduced oxidative damage by increasing glutathione (GSH) levels and decreasing malondialdehyde (MDA), a marker for oxidative stress; an increase in GSH protects cells from free radicals (Fathizadeh et al., 2020). A dose of 3000 mg per day of this supplement in patients with sepsis contributed to a reduction in oxidative stress and inflammation (Keshani et al., 2022). The researchers demonstrated that LC supplementation at doses higher than 2 g per day contributed to a reduction in lipid oxidation and inflammation and promoted the defence system's action against oxidative stress (Haghighatdoost et al., 2019).

A meta-analysis showed that LC reduces inflammatory cytokines in the blood, such as interleukin 6 (IL-6), CRP, MDA, and tumour necrosis factor-α (TNF-α), and promotes superoxide dismutase (SOD) levels in healthy patients. SOD works to reduce the damage of radicals inside the cells (Fathizadeh et al., 2020). Lebda et al. (2020) showed that carnitine protects against bisphenol A-induced hepatic toxicity, as it acts as an antioxidant and increases endogenous antioxidative defences. Carnitine contributes to the protection of mitochondria from oxidative stress, which causes mitochondrial damage and programmed cell death in various cells. LC contributes to the protection of mitochondria from oxidative stress, which causes mitochondrial damage and programmed cell death in various cells (Elkomy et al., 2020).

The antioxidant effects of LC include protection against lipid, protein, and DNA damage as well as elevated antioxidant levels (Ribas et al., 2010). LC can also be used as a metal chelator and a scavenging free radical (Ribas et al., 2012). It increases the antioxidant capacity of cardiac tissues, which has a cardioprotective effect (Mansour, 2013). Moreover, it is essential for lowering CRP, which is considered a significant risk factor in the development of CVD (Popović et al., 2014; Amirhossein, 2015).

7. L-Carnitine Clinical Findings

Several controlled human clinical studies have found that LC treatment improves cognition in humans. In a placebo-controlled, randomised, double-blinded experiment, researchers examined the effects of orally delivered LC on physical and mental exhaustion and cognitive skills in centenarians (Malaguarnera et al., 2007). Compared with those who received a placebo, centenarians who received LC exhibited significant increases in plasma total and free carnitine. LC recipients also showed substantial decreases in total fat mass and increases in total muscle mass compared with placebo recipients. Furthermore, by reducing tiredness and increasing cognitive function, this treatment regimen boosted physical and cognitive activity capacity.

In another placebo-controlled, randomised, double-blinded experiment, researchers examined the effects of orally administered LC on the clinical symptoms of autism spectrum disorder (ASD) (Geier et al., 2011). According to the researchers' clinical global impression and the results

from the Childhood Autism Rating Scale (CARS) and the Autism Treatment Evaluation Checklist (ATEC), LC treatment dramatically reduced the clinical symptoms of ASD, notably in the areas of cognitive function. In participants diagnosed with ASD who received LC, increased serum free carnitine levels were significantly associated with clinical improvements in hand muscular strength, cognitive scores, and CARS scores, whereas this association was not observed in those who received the placebo.

8. L-Carnitine and Histopathology

Histological studies have demonstrated the protective effects of LC on the liver; one of these studies showed a significant improvement in the liver tissue of mice with cancer cachexia due to inflammation after treatment with LC, as it reduced the appearance of hydropic and fatty degeneration in hepatocytes, the incidence of cellular necrosis, and the disruption of the hepatic cord (Jiang et al., 2016). LC was also shown to improve fatty liver by decreasing the accumulation of lipids in the liver cells of medaka fish (*Oryzias latipes*)) Fujisawa et al. (2017).

The effect of LC is not limited to the liver; its effect is also observed in the kidneys, where it has shown renoprotective effects in patients with chronic tacrolimus nephropathy (TAC) in the kidney tissue in general and on mitochondria in particular. The treatment of rats with TAC led to an improvement in the infiltration of inflammatory cells, the thickness of the glomerular basement membrane, and an improvement in the renal tubule vacuoles and tubulointerstitial fibrosis. In addition, LC modified programmed cell death. At the ultrastructure level, treatment with LC showed restoration of the mitochondria in terms of their number, size, and function. TAC destroyed mitochondrial structures and their cristae because of their high consumption of oxygen, which leads to oxidative stress, and treatment with LC led to the elimination of oxidative stress (Zheng et al., 2021).

A study in male rats with cirrhosis showed that the administration of LC with branched-chain amino acids (BCAAs) protected hepatocytes by reducing hepatocyte damage through lipotoxicity suppression, enhancement of lipolysis, and an increase in cytoprotective index species (LysoPE). In addition, LC treatment with BCAA contributed to the inhibition of the activity of hepatic stellate cells and hepatic macrophages caused by the extracellular vesicles of damaged hepatocytes (Tamai et al., 2021).

LC led to a significant improvement in the renal histological structure by reducing the incidence of distortion, inflammation, and interstitial haemorrhage resulting from the treatment of male rats with monosodium glutamate (Koohpeyma et al., 2021).

One of the protective effects of LC is that it contributes to the reduction of oxidative stress induced by aspartame (ASP) in its action as an antioxidant through three mechanisms described by Surai (2015). First, its acts as a free radical scavenger. Second, it inhibits the enzymes responsible for the production of free radicals, thus preventing the formation of free radicals. Third, it works under the conditions of oxidative stress to maintain the electrical transport chain of mitochondrial integrity and contributes to the maintenance of the optimal redox state of the cell by activating antioxidant enzymes and non-enzymatic antioxidants. Therefore, the beneficial effect of LC appeared in the partial recovery of the cardiac muscle with slight congestion in the muscle fibres, as the treatment with ASP led to a disturbance of the cardiac muscle fibres and a distortion in the size and shape of its nuclei (Al-Eisa et al., 2018).

LC showed cardioprotection in isoproterenol-treated rats by reducing the infiltration of inflammatory cells in myocardial fibres, improving the structure of these fibres, and significantly decreasing the level of fibrosis resulting from isoproterenol treatment (Emran et al., 2021).

9. L-Carnitine and COVID-19

LC is a vital and natural component of cells that aids in fatty acid oxidation in the mitochondria; lowers cholesterol, LDL, and TAG; and raises HDL. The severity of coronavirus disease 2019 (COVID-19) is related to dyslipidaemia (Wei et al., 2020). However, new research has demonstrated that LC has significant antioxidant and anti-inflammatory properties, as shown in Figure 3 (Modanloo and Shokrzadeh, 2019). It helps modify the mechanisms of several body systems, such as the nervous and immune systems, and reduces inflammatory factors; thus, antioxidant therapy contributes to strengthening the immune response and improving glutathione levels and oxygenation rates in the body (Soto et al., 2020). Therefore, antioxidant supplementation is recommended as a treatment for COVID-19 (Derouiche, 2020)

LC treatment of human lung epithelial cells infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in vitro has been shown to reduce inflammation through the downregulation of angiotensin-converting enzyme 2 (ACE2), a major host-dependence factor (Bellamine et al., 2021).

No clinical studies have demonstrated a relationship between LC and protection against infection with coronaviruses, but the protective role of LC in protection against COVID-19 was demonstrated using Mendelian randomisation, in which genetic predisposition reduced susceptibility to COVID-19 when carnitine levels were elevated (Li et al., 2021).

A considerable percentage of individuals infected with SARS-CoV-2 develop chronic fatigue syndrome, which can last for months. Despite this, no specific therapy for post-disease fatigue has been discovered. However, several clinical investigations have demonstrated the efficacy of LC in reducing fatigue induced by the treatment of several diseases, such as cancer and multiple sclerosis. As a result, it can be regarded a possible alternative for reducing COVID-19-induced fatigue, and its use is encouraged in future clinical trials to assess its efficacy and safety (Vaziri-Harami and Delkash, 2022).

Carnitine modulates the action of inflammatory cytokines, such as IL-6 and TNF-α; protects against the side effects of anti-coronavirus drugs; and prevents some damage caused by COVID-19 infection, such as pulmonary dysfunction and cardiotoxicity (Fakhrolmobasheri et al., 2021).

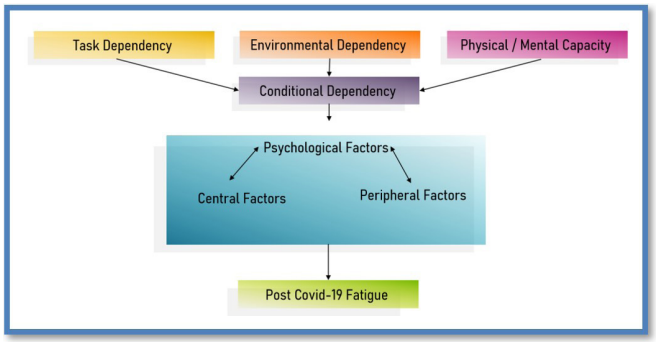

Figure 4. Factors affecting fatigue after COVID-19 (Rudroff et al., 2020).

Post-infection fatigue occurs often in both viral and nonviral disorders (Poenaru et al., 2021). As a result, many patients with COVID-19 experience post-disease fatigue. According to Rudroff et al. (2020), fatigue caused by COVID-19, defined as a decline in physical and mental activity, may be the result of changes in the central, peripheral or psychological factors. These factors depend on conditional dependencies, such as the tasks a person performs, the environmental conditions in which the tasks are performed, and the person's physical and mental abilities (Figure 4).

Observational studies have revealed that the symptoms of COVID-19 linger for approximately 21 days from the onset of the disease, with some individuals experiencing symptoms for up to 4 months. Shortness of breath and anosmia are the most common symptoms reported, which can last for over 3 weeks. The aetiology and pathophysiology of fatigue following COVID19 are unknown, although central and peripheral mechanisms are thought to play a role in the development of fatigue. The cytokine storm can lead to fatigue by causing inflammation and starvation, followed by muscular loss, weakness, and weariness. Furthermore, when the immune system is engaged, infection raises baseline energy consumption (Virgens et al., 2021).

10. Conclusion

Carnitine as a dietary supplement has been touted as therapeutic for a variety of illnesses involving human carnitine deficiency and impaired fatty acid oxidation, implying that nutritional or pharmacologic carnitine supplements may be advantageous in some conditions. Because individuals' nutrient needs may exceed their nutrient intake from food in some illnesses and health conditions, carnitine is classified as a conditionally essential nutrient. Because LC has low absorption and bioavailability, a high renal clearance, and active uptake into tissues, it is difficult to increase LC levels in the plasma to 2 mg or above with oral administration. When kidney function is not affected, intravenous delivery of LC may be more effective, as more than 95% of LC filtered via the glomeruli is retained, and excess exogenous LC is rapidly eliminated once the active transporters are saturated. Carnitine is a natural chemical that is nontoxic at oral levels up to several grams; therefore, supplements are frequently advised for primary and secondary deficits. Supplemental consumption of carnitine is generally tolerated because it is easily eliminated.

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