Carnitine and its derivatives as a potential option for cardiovascular, neurologic, and metabolic complications of COVID-19

ABSTRACT

As a multisystem disease, COVID-19 and its treatment demonstrate a wide variety of complications. Carnitine is a non-essential amino acid derivative that plays an essential role in the metabolism of fatty acids and alleviates inflammation and oxidative stress. We investigated the possible role of carnitine and its derivatives in COVID-19-induced fatigue, cardiovascular, neurological, and reproductive system complications. A thorough literature search was performed using the keywords and their synonym words including COVID-19, SARS-CoV-2, SARS, MERS, Carnitine, and L-Carnitine. Non-English literature and conference abstracts were not included. Animal experiments were excluded unless supporting the basic evidence for carnitine efficacy. Oxidative stress and Inflammatory factors are vital in cellular injury pathways caused by COVID-19. Carnitine and SARS-Cov-2 followed common cytokine and stress oxidative-related cellular pathways. Carnitine may act as a protective antioxidant against SARS-Cov-2 infection by modulating proinflammatory cytokines. Considering the safety profile of carnitine, it may have promising clinical results in alleviating COVID-19 severity and its complications.

Keywords: *COVID-19, SARS-CoV-2, COVID-19 drug treatment, carnitine, cytokine, Oxidative stress*

INTRODUCTION

Since the initial reports of COVID-19 in China, the virus has infected almost 190 million people, claiming over 4 million deaths. [1]. While COVID-19 is primarily a respiratory illness, its complications impact various body systems. [2–4]. It is speculated that the severity of the infection, and cytokine storm, might play a significant role in disease complications [5].

Various groups of medications that target different pathways of virus function were examined for the treatment or alleviating the symptoms of COVID-19 infection. There has been growing interest in using drugs that act on inflammatory factors in patients with hyperinflammatory states, including corticosteroids and Interleukin-6 inhibitors [6].

Carnitine is an essential amino acid derivative [2] and a water-soluble micronutrient that may have a promising effect on COVID-19 [7]. The human body can obtain carnitine either through food or endogenous resources[8]. It is synthesized from trimethyl-lysine in the kidney, liver, and brain [9] and is found abundantly in the heart, kidney, liver, and skeletal muscle[10]. The beneficial effect of carnitine and its active stereoisomer, acetyl L-Carnitine, on some body systems that are insulted with COVID-19 has been demonstrated in other settings in various

clinical studies (Table 1) [2,11]. This micronutrient plays a vital role in the metabolism of fatty acids in cells and has protective effects on cell membrane structure [12]. L-Carnitine controls neurotransmitter regulation[13], decreases proinflammatory cytokines like TNF-∝, IL-1, and IL6 [14,15], and reduces oxidative stress and inflammation [7]. A significant number of patients with COVID-19 suffer from its sequels on cardiovascular, neurologic, fertility systems, and the chronic fatigue syndrome that may persist for months after the infection.

Nevertheless, no particular treatment has been found. At the same time, many clinical trials have shown the effectiveness of l-carnitine in relieving fatigue caused by treating diseases such as cancer, MS, and many other diseases. Considering the beneficial effects of L-Carnitine in settings other than COVID-19, this study aimed to review the potential benefits of L-Carnitine supplementation in patients with COVID-19.

METHODS

We performed a thorough literature search using the keywords and synonym words, including COVID-19, SARS-CoV-2, SARS, MERS, Carnitine, and L-Carnitine. PubMed, Google Scholar, BioRxiv, Clinical Trials in NIH (National Institute of Health) were used as electronic databases to retrieve all the studies about the use or effect of carnitine supplementation in COVID-19. No time limitation was applied, and a bibliographical search was done to retrieve all the current basic and clinical evidence related to the symptoms of COVID-19, for which efficacy of carnitine has been discussed or proposed. We did not include non-English literature and conference abstracts. Animal experiments were excluded unless supporting the basic evidence for carnitine efficacy.

CARNITINE AND COVID-19

Currently, three clinical trials have been registered regarding the efficacy of Carnitine in COVID-19 patients [16–18]. Altay et al. found that carnitine significantly decreases the recovery time in mild to moderate COVID-19 patients [19]. Another research published in The Lancet journal revealed that higher serum acetyl-Carnitine and Carnitine concentrations protect against severe COVID-19 and associated hospitalization. This study showed the highest protective effect in hospitalized compared to non-hospitalized COVID-19 patients using mendelian randomization analyses [20].

A recent randomized placebo-controlled clinical trial concluded that combined metabolic cofactors, including L-carnitine, significantly accelerate recovery in the mild-moderate COVID-19 patients than placebo (6.6 days vs. 9.3 days). They used 7.46 g daily L-Carnitine (combined with L-serine, N-acetyl-L-cysteine, and nicotinamide riboside) and hydroxychloroquine for 14 days. Hydroxychloroquine treatment duration was five days. Moreover, a significant decrease in the AST, ALT, and LDH levels has been noted after 14 days. There were just a few minor side effects that did not need medical attention. [19]

CARNITINE AND COVID-19-TREATMENT-INDUCED ADVERSE EFFECTS

L-Carnitine is transported to the mitochondria via organic cation transporters (OCTs) for long-chain fatty acid oxidation. OCTs have broad overlapping substrate selectivities [21]. Organic Cation Transporter Novel 2 (OCTN2) has a critical role in the cellular uptake of carnitine in most tissues.

The imbalance in Carnitine levels induced by some medications can negatively affect various organs' function and lead to cardiovascular diseases. Diseases such as rheumatoid arthritis, Crohn's disease, and asthma have been seen in OCTN gene variations [22].

Rödin et al. in 2020 showed that the majority of COVID-19 drugs in clinical trials could inhibit this transporter [23]. Notably, remdesivir has a 63% inhibitory effect on this transporter, which can cause Carnitine deficiency and further complications [23]. Considering the inhibitory effects induced by the medications used in various clinical trials, the probability of Carnitine deficiency in COVID-19 survivors and carnitine's use would be important.

CARNITINE AND COVID-19-INDUCED CARDIOVASCULAR COMPLICATIONS

Cardiovascular complications, as the second leading cause of death after respiratory failure in patients with COVID-19 infection [24], occur in almost 30% of hospitalized patients [25,26], with a higher risk in patients with hypertension or diabetes [25]. COVID-19-induced heart failure due to increased levels of angiotensin II, cardiogenic shock, tachyarrhythmia, thrombosis and coagulation, acute coronary syndromes, cardiomyopathy, and death due to heart failure have all been reported [24,25].

Oxidative stress and inflammation in SARS-CoV-2 infection are studied through hallmarks of apoptosis, overexpression of mitochondrial genes, and upregulation of oxidative stress-responding genes [4]. SARS-CoV-2 infects myocytes through angiotensin-converting enzyme 2 (ACE2) receptors [24–26] and produces reactive oxidative species (ROS), pro-oxidant enzymes (e.g., NADPH oxidase) [27], and Nuclear Factor Kappa B (NF-kB) [4,27]. Inhibiting Nuclear Factor 2 (Nrf2) pathway and intensifying NF-kB toll-like receptor (mainly TL4) signaling pathway are among the proposed mechanisms for SARS-CoV-2 infection [4].

Carnitine supplementation neutralizes the angiotensin II-induced oxidative activity and inflammatory responses by inhibiting NADPH oxidase activation, ROS generation, NF-kB translocation to the nucleus [7,28], and regulating fatty acid transport and metabolism in mitochondria of cardiac cells [7]. A single dose of 2g carnitine in healthy participants boosted the levels of superoxide dismutase, glutathione peroxidase, catalase, and total antioxidative capacity after the first 3.5 hours [29]. Taking 0.2-4 g/day L-Carnitine with follow-up periods of 5 days to 48 weeks can significantly lower the levels of inflammatory biomarkers, including C-reactive protein, interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), and malondialdehyde, especially in immune system-compromising diseases [30,31]. Also, 1.5 – 6 gram daily L-carnitine with follow-up periods of 7 days to 3 years improved the clinical symptoms of chronic heart failure[32].

Carnitine deficiency is associated with cardiomyopathy and cardiac arrhythmia [33]. Mutations in the organic cation transporter2 (OCT2) gene or its inhibition by medications like remdesivir result in cardiomyopathy and heart failure via endogenous carnitine depletion [7,23]. Carnitine supplementation improves dilated cardiomyopathy [34], hyperlipidemia, hyperglycemia, and hypertension [7,28]. Given that metabolic disorders are risk factors for severe COVID-19, carnitine may be a supplement option for COVID-19 mortality reduction and preventive objectives.[19,7]. Studies have shown an association between HDL and LDL levels and the severity of COVID-19, with triglyceride

levels showing controversial results [35]. L-Carnitine therapy resulted in a lower rise in triglyceride levels in COVID-19 patients compared to the placebo arm. [19]. Moreover, oral carnitine has improved adult dilated cardiomyopathy in doses between 1-6 g/day for up to 6 months [34].

CARNITINE AND COVID-19-INDUCED FATIGUE

Physical or mental exhaustion occurs during or after a wide range of medical conditions, even without other accompanying mental problems [36]. Acute or persistent fatigue following SARS-CoV-2 infection is seen among more than 40% of patients and is considered one of the most common symptoms after fever [6,24,37]. Fatigue may be influenced by central, environmental, or psychological factors, conditional dependence (the type of the performing task, the environmental conditions, and the mental and physical capacity of the individual).

The exact pathophysiology and etiology of COVID-19-induced fatigue have not been well understood. Some studies believed that it might be a consequence of fever and immune response [5,37,38].

Higher IL-6 and IL-2 and the presence of single nucleotide polymorphisms in cytokine genes of IL-6, TNF-α, interferon-γ, and IL-10 in COVID-19 can affect the occurrence of complications, including fatigue and pain [5]. Several studies showed that carnitine could decrease the level of IL-6 [30,31]. On the other hand, considering the role of carnitine as a micronutrient in lipid metabolism, decreased levels of carnitine are speculated to disturb the metabolism of long-chain fatty acids and result in low energy levels and fatigue [39,40].

There have been numerous clinical studies on the efficacy of carnitine in patients with fatigue as a secondary complication of their underlying disease. In a controlled clinical trial by Cruciani et al., administration of L-Carnitine for two weeks in 29 patients with various types of advanced cancer and Carnitine deficiency state has shown positive effects on improvement of fatigue as well as increasing the blood Carnitine level. Oral carnitine was used in a three-step regimen to reduce possible nausea and vomiting (0.5 g/day for two days, then 1 g/day for two days, and 2 g/day for the last 10 days) [39]. In a randomized controlled clinical trial, Brass et al. showed that administering 10-40 mg/kg intravenous Carnitine three times per week in 183 end-stage renal disease patients for 24 weeks reduced fatigue significantly without showing any adverse effects. It was assumed that the effect of carnitine on metabolism in muscle cells might be the reason for this improvement [41]. In another trial, significant physical and mental fatigue improvement without any adverse effects was seen in patients older than 70 years after using 2g L-acetylcarnitine twice a day for six months [42]. The same effect was observed with the administration of 2 gram once daily L-carnitine for six months in centenarians[43]. Using carnitine to improve the lack of energy in COVID-19 survivors who experience chronic fatigue can be a safe and cheap choice. To the best of our knowledge, no clinical trials have been carried out to investigate the effect of L-carnitine on patients with COVID-19 experiencing fatigue. It is recommended to consider L-carnitine as a treatment option for covid-19-induced fatigue.

CARNITINE AND MENTAL HEALTH IN COVID-19 PATIENTS

Recovered patients from COVID-19 infection might suffer from insomnia, depression, post-traumatic stress disorder (PTSD), concentration and memory problems, and anxiety as long-term complications [24]. Some case

reports of cognitive impairment among recovered patients [44]. Impaired mental health in COVID-19 patients can be due to direct damage caused by the virus, indirect immune response, or adverse effects of immunotherapy [24]. Moreover, single nucleotide polymorphisms in IL-6, TNF-α, interferon-γ, and IL-10 genes can also affect the occurrence of neurocognitive complications [5].

Carnitine has been studied in several settings of mental disturbances, including cognitive impairment and depression. Preclinical research in cells and animal models has demonstrated neurotransmitter regulation, neuroplasticity induction, and membrane modulation as possible mechanisms for carnitine's anti-depressive effects [13]. L-acetylcarnitine is proposed as a possible biomarker for diagnosing and severity of major depressive disorder in humans [45]. Females and patients with childhood trauma or emotional negligence tend to have lower levels of L-acetylcarnitine [45].

Several studies have assessed the effect of L-acetylcarnitine in improving cognitive impairment [46] and its anti-depressive effects [45]. Few randomized clinical trials have studied comparative anti-depressive effects of 1-3g/day acetyl L-Carnitine against placebo, fluoxetine, or amisulpride for 40 to 84 days as the shortest and most prolonged period of studies. These studies suggest better effects and fewer adverse effects of carnitine than fluoxetine and amisulpride, making it a suitable choice, especially for older people with higher sensitivity to fluoxetine's adverse effects [13].

Carnitine may improve cognitive ability by reestablishing the synaptic function, improving cholinergic activity and mitochondrial metabolism and, protecting against oxidative stress [47]. The use of L-acetylcarnitine 2g per day for three months had shown significant improvements in the cognitive ability assessment tests of patients with mild cognitive impairment. This double-blind study verified positive results in verbal, memory, attention, and behavioral tests [48]. A meta-analysis of clinical trials concluded that L-acetylcarnitine might help patients with cognitive impairment. The included studies had a duration of 3-12 months and used 1.5–3.0 g/day of L-acetylcarnitine in their studies [46]. A blinded placebo-controlled clinical trial showed that 250 mg carnitine for 12 weeks could significantly improve the mental health parameters[49]; While the evidence of the effect of carnitine in cognitive impairment may not be enough to make firm conclusions, it can be a pretty safe supplement to be recommended in COVID-19 patients.

CARNITINE AND MALE REPRODUCTIVE SYSTEM IN COVID-19

There have been reports of orchitis and testicular pain in patients with COVID-19 [50]. Although no microscopical autopsy was performed on the patients' testicles, considering the similarity of COVID-19 to SARS and MERS on signs and infection patterns, it assumes possible testicular and germ cells damage [50]. Studies showed an association between orchitis and male infertility viral infections, including human immunodeficiency virus, hepatitis B virus, and mumps virus [50]. ACE2 receptors are highly expressed in testicular tissue[50]. Binding the SARS-CoV-2 to these receptors initiates an inflammatory cytokine cascade that affects germ cells responsible for regulating spermatogenesis and steroidogenesis. Interestingly, lower levels of ACE2 have been detected in infertile men [51]. The effect of ACE2 in ROS overproduction may also lead to injury of the male reproductive system, but since no

virus was detected in testes by RT-PCR, the mechanism of direct injury by virus remains unclear [51]. Reports of detecting the RNA of the virus in semen are rare, leaving the probability of spermatozoa injury by SARS-CoV-2 controversial [51].

Various clinical trials have studied the effects of L-Carnitine and L-acetylcarnitine on semen parameters. A systematic review of randomized clinical trials demonstrated that the use of L-Carnitine and L-acetylcarnitine significantly increases sperm motility in patients with idiopathic oligoasthenoteratozoospermia [52]. Although the exact etiology of oligoasthenoteratozoospermia stays unclear, oxidative stress seems to play an essential role in its incidence [52]. Antioxidant and protective effects of carnitine in mitochondria appear to be a possible explanation for its efficacy in these patients [52].

CONCLUSİON

Many uncertainties regarding the precise beneficial effects of present pharmacologic treatments for COVID-19 [3], the concerns on possible virus mutations [53–56], and vaccination hesitancy [57], highlights the need for improvement of the management strategies. Carnitine has shown beneficial effects on cardiovascular, neurologic, and reproductive systems and disease-induced fatigue in non-COVID-19 settings. Carnitine acts on similar cytokine and stress oxidative-related cellular pathways with SARS-Cov-2. Moreover, no serious adverse effect is reported with carnitine. While more clinical studies are needed to make a firm conclusion or recommendation, measurement of plasma levels of carnitine to identify carnitine deficient patients and supplementation with carnitine could be recommended for COVID-19 patients and survivors to alleviate COVID-19 symptoms and complications.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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Table1. Some clinical studies conducted on the use of L-Carnitine on shared clinical manifestations with COVID-19

Authors	**Shared clinical manifestation**	**Type of study Number of patients**	**Dose and a follow-up period of LC**	**Main findings**
Xiaolong Song, et al.,[32]	Cardiovascular	Meta-analysis	1.5 to 6 g/day and follow-up periods from 7 days to 3 years	LC is effective in improving the clinical symptoms of heart failure
Hamidreza Jamilian, et. al.,[49]	Mental health	A randomized, double-blind, placebo-controlled trial	250 mg carnitine supplements or placebo for 12 weeks	carnitine use for 12 weeks in patients with PCOS improved mental health parameters.
Mariano Malaguarnera, et. al.,[43]	Fatigue	A randomized and controlled clinical trial	2 g levocarnitine once daily for 6 months	Use of Carnitine shows improvement of physical and mental fatigue and cognitive function
Xuebao Zhang, et al.,[52]	Reproductive system	A systematic review and meta-analysis	3-50 g/day LC+LAC for 12-24 weeks	Use of Carnitine shows improvement of some infertility parameters in

males

LC: L-carnitine
PCOS: polycystic ovary syndrome
LAC: L-acetyl carnitine