Journal of Medicine and Public Health

ISSN: 2766-8355

Review Article

A Review of Possible Supplements to Relieve the Symptoms of Fatigue after COVID-19

Boglárka Bernadett Tisza[1], Gyöngyi Iván[2], Viola Keczeli[1], Melinda Kóró[1], Patricia Szántóri[1], Zsófia Gyócsiné Varga[1], Henriett Müller[1], Olivia Pribéli[1], Zoltán Szabó[1], Zsófia Verzár[1], Monika Sélleyné Gyuró[3], Andrea Gubicskóné Kisbendek[1] and Tímea Stromájer-Rácz[4]*

[1]*Institute of Nutritional Sciences and Dietetics, Faculty of Health Sciences, University of Pecs, Hungary*

[2]*National Institute for Infectology and Hematology, South-Pest Hospital Centre, Hungary*

[3]*Institute of Health Insurance, Faculty of Health Sciences, University of Pecs, Hungary*

[4]*Institute of Diagnostics, Faculty of Health Sciences, University of Pecs, Hungary*

Abstract

Background: The highly infectious coronavirus has become a global pandemic; the effective medication is yet to be developed. The health care system was strained; millions of people have been suffered from infection and complications. Post COVID-19 fatigue is a dominant characteristic of coronavirus infection. It affects general state of health, muscle strength, sleeping quality, mental health, and life quality. This paper is emphasizing and summarizing the potential beneficial supplementations of post COVID-19 fatigue symptoms.

Methods: The knowledge gained from PubMed and from the National Library of Medicine. Clinical studies and systematic review articles were collected in this topic.

Results: Herein, we discuss the possible therapeutic supplementations with anti-inflammatory, immunomodulatory and antioxidant effect. Vitamin complexes, trace elements, antioxidants, coenzymes, probiotics, essential fatty acids; one and creatine as amino acid derivatives have been appeared to be effective in relieving post COVID-19 fatigue symptoms.

Conclusions: Based on the data, these nutrients and supplements might be important to alleviate the post COVID-19 fatigue symptoms and they could be considered as a supportive therapy.

Keywords: Post COVID-19; Fatigue; Supplementation; Antioxidants; Probiotics; Creatine; Coenzyme Q10; Pandemic

Abbreviations and Acronyms

AMPK: AMP-Activated Protein Kinase; ADP: Adenosine Diphosphate; ATP: Adenosine Triphosphate; BFI: Brief Fatigue Inventory; CK: Creatine Kinase; CFQ-11: Chalder Fatigue Scale; COVID-19: Coronavirus Disease 2019; DHA: Docosahexaenoic Acid; DNA: Deoxyribonucleic Acid; EPA: Eicosapentaenoic Acid; FACIT-Fatigue Scale: Functional Assessment of Chronic Illness Therapy-Fatigue Scale; FIS: Fatigue Impact Scale; GABAA: Gamma-Aminobutyric Acid; MFI: Multidimensional Fatigue Inventory; NADH: Nicotinamide Adenine Dinucleotide+Hydrogen; PFS: Piper Fatigue Scale; PSQI: Pittsburgh Sleep Quality Index; PUFA: Polyunsaturated Fatty Acids; ROS: Reactive Oxygen Species; SARS-COV-2: Severe Acute Respiratory Syndrome Coronavirus-2; SOD: Superoxide Dismutase; VAS: Visual Analogue Scale; WHO: World Health Organization

Citation: Tisza BB, Iván G, Keczeli V, Kóró M, Szántóri P, Varga ZG, et al. A Review of Possible Supplements to Relieve the Symptoms of Fatigue after COVID-19. J Med Public Health. 2023;4(2):1062.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Feb 24th, 2023

***Corresponding author:** Boglárka Bernadett Tisza, Institute of Nutrition Sciences and Dietetics, Faculty of Health Sciences, University of Pecs, 3 Vörösmarty Street, Pécs, Hungary, E-mail: boglarka.tisza@etk.pte.hu

Introduction

The coronavirus outbreak began in Wuhan, China, in late 2019 and was named COVID-19 on March 11, 2020, by the World Health Organization (WHO). Since November 26, 2021, a total of 5 virus variants have already been known in the world, namely alpha, beta, gamma, delta, and omicron [1-2]. The incidence of post-COVID outcomes was 10% to 35% in outpatients and nearly 80% in- hospital patients. In hospitalized individuals, symptoms may last for eight weeks or more after discharge or more than four weeks in the case of non-hospitalization [3]. After 90 days of recovery in older adults, the most common consequence after COVID was fatigue. Overall, the incidence was 17.5% and the higher rate was 72% in hospitalized patients [4-6]. Chronic Fatigue Syndrome is a cognitive disorder (lasts more than 6 months), characterized by prolonged fatigue, muscle weakness, "brain fog", depression, unrefreshing sleep, cognitive impairment and post-exertional malaise and sleep disturbance [7].

Based on WHO classification, post-viral fatigue syndrome (current coding 8E49) is covering myalgic encephalomyelitis and chronic fatigue syndrome [8]. Drowsiness and mood are associated with changes in mental fatigue, and changes in the levels of neurotransmitters (dopamine, serotonin, and acetylcholine) can cause these symptoms [9]. The central nervous system is likely to be accessible to COVID-19 *via* the forebrain. This area is a source of neurotransmitters. Coronavirus equivalents could possibly use neuronal dissemination to penetrate into the central nervous system, although it is still unclear if COVID-19 has neuroinvasive property. As a consequence, post COVID-19 infection might influence the central nervous system's function. The changes in neurotransmitter

levels (mainly serotonin and dopamine), the inflammation, axonal conduction velocity changes are central factors, are suggested to be factors due to COVID-19 [10]. Frontal cortex hypometabolism and cerebellar hypermetabolism was found with 18F-Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) among patients with COVID-19. This was also demonstrated in patients with central nervous system disorders (encephalopathy, multiple sclerosis) associated with symptoms of fatigue [11,12]. Intracellular processes are also crucial, oxidative damage due to inflammation is occurred in this condition. Viral respiratory infections are associated with the activation of NF-κB signalling and this can cause oxidative damage during the inflammation [13]. The infection affects peripheral factors, and skeletal muscle as a target appears to be approachable for the virus, suggesting the onset of muscle pain, injury, and weakness [14,15]. Inflammation, a systematic increase in interleukins, can disrupt muscle metabolism and cause muscle loss. Increased levels of interleukin 6, an inflammatory cytokine, are associated with persistent fatigue [16]. All of these changes are likely to contribute to fatigue in patients after COVID-19. Previous review has shown that post-viral fatigue syndrome has not received medical treatment [17]. In the following, this article summarizes possible supplements and nutrient intakes to alleviate the symptoms of post-COVID-19 fatigue.

Microbiome, Probiotics

Respiratory and gut mucosa is functioning as a physical barrier against microbial invasion and penetration. Nevertheless, the role microbiome is quite outstanding, because it builds up a complex system. Microbiomes can communicate with each other and interact with synapses of gut autonomic nerve system (which is combined with neuroendocrine signalling and neuronal signals). *Via* neurons there is connection between bacteria in lumen of gastrointestinal tract and the central nervous system. This gut-brain axis creates homeostasis with a communication *via* several pathways including the enteric nervous system and immune system. This system could be a significant key for the treatment of neurological disorders due to this diversified connection [18]. The connection between microorganisms of the lungs and the intestine also forms an axis to the central nervous system which is a bidirectional system [19]. According to the principle of gut-lung cross talk, lung infections and inflammations trigger dysbiosis which can disturb gut microbiota [20]. Based on previous data collection, chronic fatigue syndrome and the intestinal microbiotic ecosystem are interrelated, and probiotic supplementation (eg: *Lactobacillus casei*, *Bifidobacterium infantis*) also appeared to be beneficial in this condition [21-22].

Dysbiosis (an imbalance in the function and composition of intestinal microbiota associated with various diseases) and increased opportunistic pathogens were observed, and it was shown that the composition of intestinal microbiota in recovered subjects was significantly different.

After the resolution of COVID-19, the immunomodulatory gut commensals in fecal samples (*Eubacterium rectale*, *Faecalibacterium prausnitzii* and bifidobacterial species) remained low and depleted up to 30 days. Dysbiosis and inflammatory cytokine levels were strongly associated with disease severity [23].

The elevation of inflammatory cytokines (IL-2, IL-7, IL10, TNF α) are linked with a specific gut microbiome pattern [24]. Lower abundance of *Lactobacillus*, *Bifidobacterium*, *Bacteroides* and *Faecalibacterium* in COVID-19 patients was also presented in a systematic review [25].

Recovery from SARS-CoV-2 resulted in symbiont depletion and dysbiosis. The abundance of *Faecalibacterium prausnitzii* and the severity of the disease showed an inverse relationship. *Clostridium hathewayi* and *Clostridium ramosum* showed a positive correlation with the severity of COVID-19, however, a negative correlation was observed between *Alistipes onderdonkii* and *Faecalibacterium prausnitzii* (anti-inflammatory bacteria) and the severity of COVID-19 [26]. The richness of the microbiota does not recover even after six months of convalescence and has not returned to a stable and diverse microbial ecosystem [27].

Therefore, clarification of the significance and role of the gut-lung axis and microflora in the treatment of post COVID-19 fatigue is seemed to be a key factor. In patients with post-acute COVID-19 syndrome, the bowel microbiota showed higher levels of *Bacteroides vulgatus* and *Ruminococcus gnavus* after evaluation of the analyzed fecal microbiome. An abundance of *Bifidobacterium* and *Ruminococcus* was significantly lower in COVID-19 patients (mean 3.02% and 6.75%) than in non-COVID-19 patients (mean 16.36% and 19.22%). Furthermore, the study showed an association between fatigue and nosocomial pathogens, *Clostridium innocuum* and *Actinomyces naeslundii* ($p<0.05$). Similarly, respiratory symptoms have been associated with opportunistic bowel pathogens, fatigue, and neuropsychiatric symptoms [28].

Probiotics can contribute to the restoration of a stable intestinal microbiome and prevent the colonization of pathogenic organisms in the colon environment. Probiotics may increase barrier function in the gut and mucin secretion may inhibit the invasion of pathogenic strains [29,30].

Table 1 is summarizing some studies and different cases to assess the impact of probiotics on fatigue. The effect of Lactobacillus acidophilus NCFB 1748, *Lactobacillus paracasei* ssp. *paracasei* F19 and *Bifidobacterium lactis* Bb12 was assessed in 15 patients with chronic fatigue syndrome. The product of the mentioned strains contained 108 colony forming units/ml. The open pilot study was 10 weeks long, the first 2 weeks had an observational purpose. In the 4 weeks treatment and the 4-week long follow-up period Visual Analogue Scales (VAS) and SF-12 Health Survey were used to assess the physical activity, fatigue and health [31].

Parate and co-workers conducted case series (8 patients) with a 14-day long probiotic supplementation and multi-enzyme complex supplementation as treatment for fatigue [32]. Based on the results of a randomized, 2-arm, parallel, double-blind, placebo-controlled study, a 14-day probiotic supplementation and systematic enzyme treatment alleviated fatigue in the test arm compared to controls (91% *vs.* 15%) [33]. In this study the supplementation (probiotic and multi-enzyme complex) was conducted with the same products as in the previous case series. Oral probiotic supplements of 2 capsules (5 billion CFU / capsule) from Bacillus subtilis PLSSC (ATCC SD 7280), *Bacillus coagulans* LBSC (DSM 17654) and *Bacillus clausii* 088AE (MCC 0538) were administered. The systematic multi enzyme treatment (500 mg per capsule) contained the following: serratiopeptidase, lysozyme, bromelain, peptidase, amylase, catalase, papain, lactoferrin and glucoamylase. These enzymes have immunomodulatory properties and surmounting the oxidative stress mechanisms [34,35]. Scores on the CFQ-11 (Chalder Fatigue Scale) Likert scale decreased in both arms. Overall, the subject receiving adjunctive therapy showed a significant reduction in mental fatigue and physical scores. The study showed the effectiveness of 14-day probiotic and multi-enzyme formulation supplementation.

Table 1: Some clinical studies about probiotics is showing the relieving impact on fatigue.

Authors	Study design	Number of patients	Dosage	Results
Sullivan et al. [31]	Open pilot study	15 patients with chronic fatigue syndrome	In the treatment of 4 weeks, probiotics were administered twice daily (2 dl x 2) 108 CFU/ml	6 out of 15 patients improved based on the assessment. The neurocognitive functions improved in VAS
Parate and Shah [32]	Case series	8 patients with post COVID-19 fatigue (6 males and 2 females)	Supplementation for 14 days (2 capsules of multi-enzyme formulation twice daily) (2 capsules of probiotics once daily - 5 billion CFU / capsule)	Comparing to the baseline scores (26.63) of Chandler Fatigue Scale, in the 14th day (2.75) significant improvement appeared
Rathi et al. [33]	Randomized, 2-arm, parallel, double-blind, placebo-controlled study	100 patients in test arm and 100 patients in control arm, the patients recovered from acute COVID-19 disease	Supplementation lasted 14 days, Test arm received daily 2 capsules of probiotic supplementation and 4 capsules of multi-enzyme complex. The control arm received daily placebo with same dosage (5 billion CFU / capsule)	The supplementation alleviated fatigue in the test arm compared to control arm (91% *vs.* 15%) Chandler Fatigue Scale scores decreased in both arms
Lee et al. [36]	double-blind, randomized controlled design study	30 subjects with irritable bowel syndrome and with fatigue took part in the study	3 groups (high-dose; low-dose and placebo) received 2 capsules for 8 weeks (10 billion colony-forming units/capsule)	VAS and MFI scores improved significantly in high-dose group compared to the placebo

In a randomized controlled clinical trial, the effect of synbiotics on fatigue in irritable bowel syndrome was assessed [36]. The capsules contained 10 billion colony-forming units of six strains (two strains of *Bifidobacterium* (*bifidum* and *longum*) and *Lactobacillus* (*rhamnosus*, *acidophilus*, *casei*, *bulgaricus*, *plantarum* and *salivarius*). The capsule also contained fructo-oligosaccharides and inulin powder as prebiotics. Three groups received capsules for 8 weeks in the following way: high-dose group took 2 capsules of synbiotics; the low-dose group got 1 capsule of placebo and 1 capsule of symbiotic; the placebo group got 1 capsule of placebo. Multidimensional Fatigue Inventory (MFI) and fatigue Visual Analogue Scale (VAS) were used in the study to observe the impact.

Previous studies have already shown that probiotics can reduce extreme levels of cytokines to balance immune responses. Some of them have anti-inflammatory properties; therefore, they can modulate the immune system, which is linked to the symptoms of fatigue [37].

Creatine

In the year of 2021, a review summarized the importance of the possible pharmacological efficacy of creatine in post-viral fatigue syndrome [38]. Glycine, arginine, methionine is essential for the synthesis of this molecule. The role of the creatine kinase/creatine phosphate/creatine system in energy metabolism is often overlooked. Creatine kinase contains 4 isoforms in cytosolic forms and mitochondrial isoforms [39]. The cytosolic M-creatine kinase (M is a muscle) and B creatine kinase (B is the brain) isoforms combine dimers to form MM, MB, and BB-CK forms. Each catalyzes the reversible transfer of the γ-phosphate group of ATPs, which forms ADP and produces creatine phosphate in muscle tissue [40].

Creatine can possibly be a mediator of neuroprotection in a wide range of neuropathological conditions; it is an agonist of GABAA receptors, regulates glutamatergic transport and mediates neuroprotection [41]. It can inhibit the mitochondrial permeability transition pores; thus, the ATP level is stabilized in neurons by the stimulating production of phosphocreatine [42].

Creatine can be a suppressor of inflammation by downregulating membrane proteins in immunity [43]. Oxidative stress also can be a contributor of idiopathic chronic fatigue [44]. Creatine as an antioxidant protects the mitochondreal DNA from damage caused by reactive oxygen species [45,46].

In the early 1990s, Wong et al studied muscle metabolism using 31P nuclear magnetic resonance spectroscopy in patients with chronic fatigue syndrome. Intracellular phosphate metabolism was assessed during rest, dynamic exercise, and fatigue. Compared to normal controls, intracellular adenosine triphosphate concentrations decreased relatively and reached depletion more rapidly [47].

Between 2014 and 2015, twenty-one women participated in a dietary intervention of guanidine acetic acid (a precursor of creatine) that was evaluated in a randomized, controlled crossover study. After three months of oral administration of guanidine acetic acid (2.4 g/day), there was a significant increase in muscle creatinine compared with placebo (36.3% *vs.* 2.4%). Muscle strength also showed positive changes in the supplemented group. The results of the 36-item Short-Form Health Survey showed relief from fatigue and improvement in mental and physical areas of health-related quality of life. However, they may suggest a positive effect of creatine metabolism through the addition of guanidine acetic acid precursor [48].

Urinary creatine loss has been reported to be correlated with pain and fatigue, and it is a feature of fibromyalgia [49]. This condition is a chronic disease with centralized, generalized pain sensitivity disorder, it is similar to chronic fatigue syndrome and it has the same characteristics as memory impairment, unrefreshing sleep, malaise, fatigue, and locomotor pain [50].

In a 16-week long, randomized, double-blind, placebo-controlled, parallel-group clinical trial, patients with fibromyalgia were supplemented with creatine monohydrate (20 g divided into four equal doses for 5 days, followed by 5 g daily as a single dose). The test group showed better and greater muscle strength compared to the placebo group. Supplementation increased muscle phosphoryl creatine levels. As a result, in the 36-item Short-Form Health survey the "mental health" domain was improved. The domain contained questions in connection with happiness, jitters, being worn out, feeling blue and tired. The Post Sleep Inventory questionnaire "presleep" domain also improved after the procedure. The subpart of the questionnaire emphasized falling asleep, feeling relieved while entering bed, the presence of disturbing thoughts before entering bed and falling asleep quickly [51].

Further research on the effects of creatine supplementation is needed in the future. Currently there is no evidence for an accurate outcome of therapeutic creatine intake.

The Combination of NADH and Coenzyme Q10

In the last few years, a number of pathophysiological processes

in chronic fatigue syndrome have been revealed. There is growing evidence for oxidative damage, mitochondrial dysfunction, and bioenergetic metabolic damage in the pathogenesis of chronic fatigue syndrome. NADH (Nicotinamide Adenine Dinucleotide) and Coenzyme Q10 might have decisive impact on cellular metabolism, because fatigue can be related to cellular energy systems linked to the inner mitochondrial transport processes [52]. Coenzyme Q10 (also ubiquinone) is a lipid soluble antioxidant in human mitochondria, it produces ATP and improves phosphocreatine recovery in molecules [53,54]. Coenzyme Q10 induce the activation of AMPK (AMP-Activated Protein Kinase) cascade system, which leads to the increased expression of antioxidant enzymes, like catalase and Superoxide Dismutase (SOD). As a result, it is against of the mitochondreal Reactive Oxygen Species (ROS) which induced stress damage [55]. NADH as a precursor of vitamin B3 has an antioxidant action, and also part of the glutathione-redox system, which can help with decreasing the oxidative stress [56,57]. Coenzyme Q10 and NADH- as bioenergetic cofactors for boosting mitochondrial function- could provide a potential treatment as an alternative therapy for post-viral fatigue. Table 2 is showing the supplementations in different interventions about relieving fatigue in chronic patients.

In 2012 the effect of oral supplementation of a glycophospholipid formulation combined with microencapsulated NADH and Coenzyme Q10 was assessed in patients with Lime disease [58,59]. This product also contained L-carnitine, L-tyrosine, vitamin E, minerals, alpha ketoglutaric acid, L-tyrosine *Bifido* and *Lactobacillus*. In the open label 8-week preliminary study the fatigue was evaluated with Piper Fatigue Scale (PFS). The participants took the glycophospholipid supplement with Coenzyme Q10 and NADH in a daily dose. The fatigue was monitored at 0, 7, 30 and 60 days with Piper Fatigue Scale. The change of the scores in subcategories (Behavior/severity; Affective/meaning; Sensory; Cognitive/Mood) of PFS was assessed.

In 2012 Castro-Marrero and co-workers evaluated the benefits of NADH and Coenzyme Q10 supplementation. During the study the study the biochemical parameters (ATP level, citrate synthase, NAD+/NADH and Coenzyme Q10) were monitored [60].

In 2021 they assessed the effects of supplementation with Fatigue Impact Scale (FIS-40) Pittsburg Sleep Quality Index (PSQI) and 36-Item Short Form Health Survey [61]. The cognitive domain improved significantly at the 4- and 8-week visits compared to the baseline. The FIS-40 was divided into three domains, psychosocial functioning (20 items), physical (10 items) and cognitive (10 items).

Coenzyme Q10 and NADH deficiency has been observed among patients with chronic fatigue syndrome/fibromyalgia, the supplementation of these two molecules is reported to be safe and their consumption is appropriate to alleviate post viral fatigue [62,63].

Other Potential Supplements

Other macro- and micronutrients appeared to have a notable effect on the symptoms of fatigue. Due to the controversial origin and pathophysiology of post-viral fatigue there can be association between the modified nervous and immune system activities [64]. It is also known that nutritional supplement with plant extracts, vitamins and minerals ameliorated fatigue and quality of life in post-operative and oncological conditions [65].

The impacts of complex nutritional supplement with 19 nutrients were evaluated in an observational study to improve chronic fatigue after SARS-CoV-2 infection [66]. The product contained vitamin complexes (vitamin B1, C, D and vitamin E), amino acids (arginine and carnitine), sucrosomial minerals (zinc, magnesium, iron, iodine and selenium), antioxidants (Lycopene and Coenzyme Q10) and plant extracts (100 mg Panax ginseng and 50 mg *Eleutherococcus senticosus*). Improvement in general health was the main consideration among COVID-19 negative subjects with symptoms of chronic fatigue. One sachet supplementation's effect was assed as a daily dose after 28 days. The main goal was to estimate the fatigue recovery of patients, which was defined as an increase of at least 5 units in FACIT-Fatigue scale (Functional Assessment of Chronic Illness Therapy-Fatigue). Among the 181 subjects the results of FACIT-Fatigue scale visibly improved at least 1 unit after 28 days in 90.05% of subjects. A 10-unit improvement was found in half of the subjects after 28 days.

L-carnitine is an amino acid derivative, which has an important role in energy metabolism. As a transporter for long chain fatty acids helps to produce energy [67]. Cardiac muscle and skeletal muscle utilize fatty acids as energy source; therefore, carnitine could be a treatment for muscle weakness and general fatigue. General fatigue, muscle loss and muscle weakness due to catabolic effects are characterizing chronic diseases. It has been demonstrated that L-carnitine has beneficial

Table 2: Clinical studies summarizing the effects of NADH and Coenzyme Q10 supplementations.

Authors	Study design	Number of patients	Dosage	Results
Nicolson et al. [58]	Open label 8-week preliminary study	16 patients (6 males and 10 females) with 'chronic Lyme disease' were the subjects	One serving (5 capsules) contained 35 mg NADH, Coenzyme Q10. The participants took 5 capsules in the morning and 5 capsules at night for 8 weeks	After the 8 weeks of treatment the total mean scores of PFS showed a 26% reduction in overall fatigue. The subcategories of PFS decreased between 21-26%
Nicolson et al. [59]	Preliminary open label study	58 patients (30 females and 28 males) with chronic Lyme disease, chronic fatigue syndrome/myalgic encephalomyelitis	The participants took the suggested dose per day, 5 capsules in the morning and 5 capsules at night for 8 weeks (one serving contained 35 mg NADH, Coenzyme Q10)	After the 8 weeks of supplementation 30.7% reduction in overall fatigue can be observed. The subcategories in PFS decreased between 28%-30.7%
Castro-Marrero et al. [60]	Randomized, double-blind placebo-controlled trial	39 patients (NADH+CoQ10 group) and 34 patients (placebo group) with fatigue	8 weeks of treatment with 200 mg of CoQ10 and 20 mg of NADH and matching placebo	Significant decreasing in FIS Significantly higher ATP levels and production were observed in the supplemented patients (119.24 to 31.43 nmol/mg) compared to the placebo group (67.45 to 15.1 nmol/mg)
Castro-Marrero et al. [61]	Prospective, Randomized, Double-Blind, Placebo-Controlled Trial	207 patients with myalgic encephalomyelitis/chronic fatigue syndrome 72 (intervention group) and 72 (placebo group) patients were analyzed	8 weeks of treatment with 200 mg of CoQ10 and 20 mg of NADH and matching placebo	FIS-40 scores decreased; psychosocial domain improved. In PSQI habitual sleep efficiency domain and sleep quality domain had higher scores in placebo

effect on fatigue in cancer, chronic kidney disease [68,69]. The efficacy of L-carnitine supplementation for general fatigue in cancer patients was evaluated during chemotherapy. The 11 patients administered 1500 mg/day levocarnitine per os, the change was assessed using the Brief Fatigue Inventory from the baseline to 8 weeks. As a result, the Brief Fatigue Inventory scores were significantly higher in the pre-treatment for all patients comparing to post-treatment scores (mean pre-BFI: 4.9 ± 1.8 *vs.* post-BFI: 1.2 ± 1.6). Carnitine supplementation may reduce fatigue in cancer patients; thus, it could be efficient to cope with fatigue symptoms [70].

The low level of erythrocytes' long-chain PUFAs often characterized by systematic inflammation and low antioxidant status [71]. Their role appeared during the COVID-19 pandemic as a potential treatment. The essential fatty acids have been emphasized due to their beneficial effect on modulating immune response to viral infections. The inflammatory cytokines can be influenced by dietary DHA and EPA supplementation [72]. In a clinical cohort study, Castro-Marrero et al. [60] evaluated the potential therapeutic supplementation of omega-3 fatty acids by the HS-Omega-3 Index method to alleviate chronic fatigue syndrome. In case of the 31 participants, the results showed that 92.6% of patients had a decreased omega-3 index (5.75%) and slightly higher levels of omega-6 fatty acids, although the study did not show a significant association between the Pittsburgh Sleep Quality Index and FIS-40 scores.

Low level of zinc is associated with an increased risk of viral infection, and it has been shown to play an important role in maintaining the integrity of skin and mucous membranes and it is essential for immune processes. Several studies have presented that zinc deficiency in patients with coronavirus infection was associated with a higher risk of complications [73]. Fatigue and cognitive disorders are characterized by low serum zinc concentration. In 2021, Castro-Marrero and colleagues evaluated the results of zinc and melatonin supplementation in a 16-week, randomized, placebo-controlled, double-blind study based on a demonstration concept [74,75]. 50 patients with chronic fatigue syndrome received zinc (10 mg) and melatonin (1 mg). After 16 weeks of a combination of these two supplements, the physical domain of the Fatigue Effect Scale (FIS-40) was significantly improved, and the quality of sleep was also significantly improved in both groups. Discontinued supplementation (4 weeks after treatment) resulted in deterioration of sleep latency [76-78].

Conclusions

Post-COVID-19 fatigue is a complex condition and additional research is needed to know the precise physiological details. This summary is focusing on the known possible mechanisms and the ways of potential treatments with supplementation. The data described promising outcomes in connection with the consumption of these micronutrients, albeit our list is not complete. The mentioned supplements appeared to be effective in relieving fatigue after infection of COVID-19.

The intake of probiotics seemed to be highlighted in order to restore the intestinal microbiome. Probiotics could affect mental health *via* the intestinal-brain axis. The results have already shown an improvement in mental fatigue, sleeping habits and life quality. The possibilities of creatine use raise new questions. The effect of creatine should be investigated in further studies to develop a new therapy to alleviate post COVID-19 fatigue syndrome.

In multivitamin complexes, vitamin C and vitamin B complexes and magnesium are involved in energy-producing. Their role in the intracellular cofactor supplementation is key factor to improve mitochondrial function via the citric acid cycle and ATP synthesis with Coenzyme Q10. They can boost and restore bioenergetic metabolism and mitochondrial function. The ATP of depleted cells is replenished, which can help with energy production. The mostly energy-demanding central nervous system and skeletal muscle are depending on these mechanisms.

NADH plus Coenzyme Q10 showed a high antioxidant effect in alleviating oxidative stress damage in patients with chronic fatigue syndrome. L-carnitine supplementation might improve nutritional status due to anti-catabolic effect. The supplementation can increase the protein synthesis and improved the nitrogen balance. The mitochondrial function was ameliorated, consequently it prevents oxidative stress. It helps to reduce the inflammation and tissue damage. The positive effects of *P. ginseng* also known for improving memory, cognitive function, and mental fatigue.

The first pilot study of the addition of melatonin and zinc resulted in an adjuvant treatment to reduce fatigue. Doses of 10 mg zinc and 1 mg melatonin were shown to be effective. Omega-3 fatty acid levels were low in subjects with chronic fatigue syndrome, thus more interventions are needed for this replacement. Decreased levels of omega-3 fatty acids may indicate an inflammatory condition in the patient, which may be associated with fatigue. In the future the importance of omega-3 fatty acid supplementation for therapeutic purposes could be emphasized.

Vitamin D is a well-known, low-cost and safe supplement during the pandemic. Although, this nutrient does not seem to be effective against post-COVID-19 fatigue. This pandemic era reinforced the immune effects of the vitamin D. Nevertheless, it is fundamental to get more evidence to evaluate the effect of it. Selenium as a major component of antioxidant defense and mechanisms is noted to be decisive in this condition.

The immune boosting role of vitamin D, zinc, selenium and omega-3 fatty acids is a well-supported and their positive impact has been already noted. It is recommended that these oral supplements be added to improve the quality of life of patients with post-COVID fatigue. There are not too many clinical studies about the role of micronutrients and supplementations in post viral fatigue. Further investigations would be crucial about the role of micronutrients in fatigue symptoms; the results of the studies would have promising long-term benefits for this condition.

Authors' Contribution

BBT, IGy and MGyS wrote the manuscript and collected the articles. MK, SzP collected the articles and data. Supervision: AKG, TSR. Formal writing: OP, HM, ZsV, ZSz ZsGyV and VK.

References

1. Choi JY, Smith DM. SARS-CoV-2 Variants of Concern. Yansei Med J. 2021;62(11):961-8.

2. He X, Hong W, Pan X, Lu G, Wei X. SARS-CoV-2 Omicron variant: Characteristic and prevention. Med Comm (2020). 2021;2(4):838-45.

3. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. BMJ. 2020;370:m3026.

4. Huang C, Huang L, Wang Y, Li X., Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet.

2021;397(10270):220-32.

5. Carfì A, Bernabei R, Landi F. Gemelli AgainstCOVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. JAMA. 2020;324:(6):603-5.
6. Nagy ZZ. Ophtalmic signs and complications of the COVID-19 infection. Develop Health Sci. 2021;3(4):79-82.
7. Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. BMC Neurol. 2011;11:37.
8. WHO. ICD-11 for Mortality and Morbidity Statistics. 2023.
9. Meeusen R, Watson P, Hasegawa H, Roelands B, Piacentini MF. Central fatigue: The serotonin hypothesis and beyond. Sports Med. 2006;36(10):881-909.
10. DeLuca J, Genova HM, Capili EJ, Wylie GR. Functional neuroimaging of fatigue. Phys Med Rehabil Clin N Am. 2009;20(2):325-37.
11. Roelcke U, Kappos L, Lechner-Scott J, Brunnschweiler H, Huber S, Ammann W, et al. Reduced glucose metabolism in the frontal cortex and basal ganglia of multiple sclerosis patients with fatigue: A 18F-fluorodeoxyglucose positron emission tomography study. Neurology. 1997;48(6):1566-71.
12. Delorme C, Paccoud O, Kas A, Hesters A, Bombois S, Shambrook P, et al. Covid-19 related encephalopathy: A case series with brain FDG-PET/CT findings. Eur J Neurol. 2020;27(12):2651-7.
13. Komaravelli N, Casola A. Respiratory viral infections and subversion of cellular antioxidant defenses. J Pharmacogenomics Pharmacoproteomics. 2014;5(4):1000141.
14. Perrin, R, Riste L, Hann M, Walther A, Mukherjee A, Heald A, et al. Into the looking glass: Post-viral syndrome post COVID-19. Med Hypotheses. 2020;144:110055.
15. Rudroff T, Fietsam AC, Deters JR, Bryant AD, Kamholz J. Post-COVID-19 fatigue: Potential contributing factors. Brain Sci. 2020;10(12):1012.
16. VanderVeen BN, Fix DK, Montalvo RN, Counts BR, Smuder AJ, et al. The regulation of skeletal muscle fatigability and mitochondrial function by chronically elevated interleukin-6. Exp Physiol. 2019;104(3):385-97.
17. Sandler CX, Lloyd AR. Chronic fatigue syndrome: Progress and possibilities. Med J Aust. 2020;212(9):428-33.
18. Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, et al. The Microbiota-Gut-Brain Axis. Physiol Rev. 2019;99(4):1877-2013.
19. Budden KF, Gellatly SL, Wood DLA, Cooper MA, Morrison M, Hugenholtz P, et al. Emerging pathogenic links between microbiota and the gut-lung axis. Nat Rev Microbiol. 2017;15:55-63.
20. Dumas A, Bernard L, Poquet Y, Lugo-Villarino G, Neyrolles O. The role of the lung microbiota and the gut–lung axis in respiratory infectious diseases. Cell Microbiol. 2018;20(12):e12966.
21. Roman P, Carrillo-Trabalón F, Sánchez-Labranca N, Cañadas F, Estévez AF, Cardona D. Are probiotic treatments useful on fibromyalgia syndrome or chronic fatigue syndrome patients? A systematic review. Benef Microbes. 2018;9(4):603-11.
22. Corbitt M, Campagnolo N, Staines D, Marshall-Gradisnik S. A Systematic Review of Probiotic Interventions for Gastrointestinal Symptoms and Irritable Bowel Syndrome in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). Probiotucs Antimicrob Proteins. 2018;10(3):466-77.
23. Yeoh YK, Zuo T, Lui GC, Zhang F, Liu Q, Li AY, et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut. 2021;70(4):698-706.
24. Schirmer M, Smeekens SP, Vlamakis H, Jaeger M, Oosting M, Franzosa EA, et al. Linking the human gut microbiome to inflammatory cytokine production capacity. Cell. 2016;167(4):1125-36.e8.
25. Yamamoto S, Saito M, Tamura A, Prawisuda D, Mizutani T, Yotsuyanagi H. The human microbiome and COVID-19: A systematic review. PLoS One. 2021;16(6):e0253293.
26. Zuo T, Zhang F, Lui FCY, Yeoh YK, Li AYL, et al. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. Gastroenterology. 2020;159(3):944-55.
27. Peng J, Zhang M, Yao G, Kwok L, Zhang W. Probiotics as Adjunctive Treatment for Patients Contracted COVID-19: Current Understanding and Future Needs. Front Nutr. 2021;8:669808.
28. Liu Q, Mak JWY, Su Q, Yeoh YK, Lui GCY, Ng SSS, et al. Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome. Gut. 2022;71(3):544-52.
29. Walton GE, Gibson GR, Hunter KA. Mechanisms linking the human gut microbiome to prophylactic and treatment strategies for COVID-19. Br J Nutr. 2021;126(2):219-27.
30. Ferreira C, Viana SD, Reis F. Gut microbiota dysbiosis-immune hyperresponse-inflammation triad in coronavirus disease 2019 (COVID-19): Impact of pharmacological and nutraceutical approaches. Microorganisms. 2020;8(10):1514.
31. Sullivan Å, CE Nord, Evengård B. Effect of supplement with lactic-acid producing bacteria on fatigue and physical activity in patients with chronic fatigue syndrome. Nutr J. 2009;8:4.
32. Parate R, Shah N. Management of post COVID-19 fatigue using systemic enzymes and probiotics—Case series. Med J Clin Trials Case Stud. 2021;5(2):281.
33. Rathi A, Jadhav S, Shah N. Randomized Controlled Trial of the Efficacy of Systemic Enzymes and Probiotics in the Resolution of Post-COVID Fatigue. Medicines (Basel). 2021;8(9):47.
34. Murakami F, Sasaki T, Sugahara T. Lysozyme stimulates immunoglobulin production by human-human hybridoma and human peripheral blood lymphocytes. Cytotechnology. 1997;24(2):177-82.
35. Shi XL, Shi ZH, Feng MQ, Ye L, Zhu HY, Li JY, et al. High expression of recombinant human catalase and its immunomodulatory effects on H1N1 influenza virus infection. Process Biochem. 2013;48(4):588-92.
36. Lee SH, Cho DY, Lee SH, Han KS, Yang SW, Kim JH, et al. A Randomized Clinical Trial of Synbiotics in Irritable Bowel Syndrome: Dose Dependent Effects on Gastrointestinal Symptoms and Fatigue. Korean J Fam Med. 2019;40(1):2-8.
37. Elekhnawy E, Negm WA. The potential application of probiotics for the prevention and treatment of COVID-19. Egypt J Med Hum Genet. 2022;23(1):36.
38. Ostojic SM. Diagnostic and Pharmacological Potency of Creatine in Post-Viral Fatigue Syndrome. Nutrients. 2021;13(2):503.
39. Kazak L, Cohen P. Creatine metabolism: Energy homeostasis, immunity and cancer biology. Nat Rev Endocrinol. 2020;16(8):421-36.
40. Wyss M, Kaddurah-Daouk R. Creatine and creatinine metabolism. Physiol Rev. 2000;80(3):1107-213.
41. Koga Y, Takahashi H, Oikawa D, Tachibana T, Denbow DM, Furuse M. Brain creatine functions to attenuate acute stress responses through GABAnergic system in chicks. Neuroscience. 2005;132(1):65-71.
42. Beal MF. Neuroprotective effects of creatine. Amino Acids. 2011;40(5):1305-13.
43. Leland KM, McDonald TL, Drescher KM. Effect of creatine, creatinine, and creatine ethyl ester on TLR expression in macrophages. Int Immunopharmacol. 2011;11(9):1341-7.
44. Lee JS, Kim HG, Lee DS, Son CG. Oxidative stress is a convincing contributor to idiopathic chronic fatigue. Sci Rep. 2018;8(1):12890.
45. Sestili P, Martinelli C, Colombo E, Barbieri E, Potenza L, Sartini S, et al. Creatine as an antioxidant. Amino Acids. 2011;40(5):1385-96.
46. Guidi C, Potenza L, Sestili P, Martinelli C, Guescini M, Stocchi L, et al. Differential effect of creatine on oxidatively-injured mitochondrial and nuclear DNA. Biochim Biophys Acta. 2008;1780(1):16-26.
47. Wong R, Lopaschuk G, Zhu G, Walker D, Catellier D, Burton D, et al. Skeletal muscle metabolism in the chronic fatigue syndrome. In vivo assessment by 31P nuclear magnetic resonance spectroscopy. Chest. 1992;102(6):1716-22.

48. Ostojic SM, Stojanovic M, Drid P, Hoffman JR, Sekulic D, Zenic N. Supplementation with guanidinoacetic acid in women with chronic fatigue syndrome. Nutrients. 2016;8(2):72.

49. Malatji BG, Meyer H, Mason S, Engelke UF, Wevers RA, van Reenen M, et al. A diagnostic biomarker profile for fibromyalgia syndrome based on an NMR metabolomics study of selected patients and controls. BMC Neurol. 2017;17(1):88.

50. Mohabbat AB, Mohabbat NML, Wight EC. Fibromyalgia and Chronic Fatigue Syndrome in the Age of COVID-19. Mayo Clin Proc Innov Qual Outcomes. 2020;4(6):764-6.

51. Alves CR, Santiago BM, Lima FR, Otaduy MC, Calich AL, Tritto AC, et al. Creatine supplementation in fibromyalgia: A randomized, double-blind, placebo-controlled trial. Arthritis Care Res (Hoboken). 2013;65(9):1449-59.

52. Hamilton D, Jensen GS. Nutraceutical Support of Mitochondrial Function Associated with Reduction of Long-term Fatigue and Inflammation. Altern Ther Health Med. 2021;27(3):8-18.

53. Lenaz G, Fato R, Formiggini G, Genova ML. The role of Coenzyme Q in mitochondrial electron transport. Mitochondrion. 2007;7:S8-33.

54. Cooke M, Iosia M, Buford T, Shelmadine B, Hudson G, Kerksick C, et al. Effects of acute and 14-day coenzyme Q10 supplementation on exercise performance in both trained and untrained individuals. J Int Soc Sports Nutr. 2008;5:8.

55. Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nat Rev Mol Cell Biol. 2012;13(4):251-62.

56. Bradshaw PC. Cytoplasmic and Mitochondrial NADPH-Coupled Redox Systems in the Regulation of Aging. Nutrients. 2019;11(3):504.

57. Santaella ML, Font I, Disdier OM. Comparison of oral Nicotinamide Adenine Dinucleotide (NADH) versus conventional therapy for chronic fatigue syndrome. P R Health Sci J. 2004;23(2):89-93.

58. Nicolson GL, Settineri R, Ellithorpe R. Glycophospholipid Formulation with NADH and CoQ10 significantly reduces Intractable fatigue in Western Blot-positive 'Chronic Lyme Disease' patients: preliminary report. Funct Foods Health Dis. 2012;2(3):35-47.

59. Nicolson GL, Settineri R, Ellithorpe R. Lipid Replacement Therapy with a Glycophospholipid Formulation with NADH and CoQ10 significantly reduces fatigue in intractable chronic fatiguing illnesses and chronic Lyme disease patients. Int J Clin Med. 2012;3(3):163-70.

60. Castro-Marrero J, Cordero MD, Segundo MJ, Sáez-Francàs N, Calvo N, Román-Malo L, et al. Does oral coenzyme Q10 plus NADH supplementation improve fatigue and biochemical parameters in chronic fatigue syndrome? Antioxid Redox Signal. 2015;22(8):679-85.

61. Castro-Marrero J, Segundo MJ, Lacasa M, Martinez-Martinez A. Sentañes RS, Alegre-Martin J. Effect of Dietary Coenzyme Q10 Plus NADH Supplementation on Fatigue Perception and Health-Related Quality of Life in Individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial. Nutrients. 2021;13(8):2658.

62. Arenas-Jal M, Suñé-Negre JM, García-Montoya E. Coenzyme Q10 supplementation: Efficacy, safety, and formulation challenges. Compr Rev Food Sci. Food Saf. 2020;19(2):574-94.

63. Alcocer-Gómez E, Cano-García FJ, Cordero MD. Effect of coenzyme Q10 evaluated by 1990 and 2010 ACR Diagnostic Criteria for Fibromyalgia and SCL-90-R: Four case reports and literature review. Nutrition. 2013;29(11-12):1422-5.

64. Klimas N, Broderick G, Fletcher MA. Biomarkers for chronic fatigue. Brain Behav Immun. 2012;26(8):1202-10.

65. Inglis JE, Lin PJ, Kerns SL, Kleckner, IR, Kleckner AS, Castillo DA, et al. Nutritional interventions for treating cancer-related fatigue: a qualitative review. Nutr Cancer. 2019;71(1):21-40.

66. Rossato MS, Brilli E, Ferri N, Giordano G, Tarantino G. Observational study ont he benefits of a nutritional suplement, supporting immune function and energy metabolism, on chronic fatigue associated with the SARS-CoV-2 post-infection progress. Clin Nutr ESPEN. 2021;46:510-8.

67. Foster DW. The role of the carnitine system in human metabolism. Ann N Y Acad Sci. 2004;1033:1-16.

68. Cruciani RA, Dvorkin E, Homel P, Culliney B, Malamud S, Shaiova L, et al. L-carnitine supplementation for the treatment of fatigue and depressed mood in cancer patients with carnitine deficiency: A preliminary analysis. Ann N Y Acad Sci. 2004;1033:168-76.

69. Fatouros IG, Douroudos I, Panagoutsos S, Pasadakis, P, Nikolaidis, MG, Chatzinikolaou A, et al. Effects of L-carnitine on oxidative stress responses in patients with renal disease. Med Sci Sports Exerc. 2010;42(10):1809-18.

70. Matsui H. Einama T, Sichi S, Kanazawa, R, Shibuya, K, Suzuki T, et al. L-Carnitine supplementation reduces the general fatigue of cancer patients during chemotherapy. Mol Clin Oncol. 2018;8(3):413-6.

71. Maes M, Mihaylova I, Bosmans E. Not in the mind of neurasthenic lazybones but in the cell nucleus: patients with chronic fatigue syndrome have increased production of nuclear factor kappa beta. Neuro Endocrinol Lettl. 2007;28(4):456-62.

72. Szabó Z, Marosvölgyi T, Szabó É, Bai P, Figler M, Verzár Z. The Potential Beneficial Effect of EPA and DHA Supplementation Managing Cytokine Storm in Coronavirus Disease. Front Physiol. 2020;11:752.

73. Shakoor H, Feehan J, Al Dhaheri AS, Ali HI, Platat C, Ismail LC, et al. Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19? Maturitas. 2021;143:1-9.

74. Castro-Marrero J, Zaragozá MC, Domingo JC, Martinez-Martinez A, Alegre J, Von Schacky C. Low omega-3 index and polyunsaturated fatty acid status in patients with chronic fatigue syndrome/myalgic encephalomyelitis. Prostaglandins Leukot Essent Fatty Acids. 2018;139:20-4.

75. Alpert PT. The Role of Vitamins and Minerals on the Immune System. Home Health Care Manag Pract. 2017;29(3):199-202.

76. Beigmohammadi MT, Bitarafan S, Abdollahi A, Amoozadeh L, Salahshour F, Abadi MM, et al. The association between serum levels of micronutrients and the severity of disease in patients with COVID-19. Nutrition. 2021;91-92:111400.

77. Maes M, Mihaylova I, De Ruyter M. Lower serum zinc in chronic fatigue syndrome (CFS): Relationships to immune dysfunctions and relevance for the oxidative stress status in CFS. J Affect Disord. 2006;90(2-3):141-7.

78. Castro-Marrero J, Cleofé Zaragozá M, López-Vilchez I, Galmes JL, Cordobilla B, Maurel S, et al. Effect of Melatonin Plus Zinc Supplementation on Fatigue Perception in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Randomized, Double-Blind, Placebo Controlled Trial. Antioxidants (Basel). 2021;10(7):1010.