Oral Supplementation for the Improvement of Fatigue Symptoms

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Fatigue, characterised by lack of energy, mental exhaustion and poor muscle endurance which do not recover following a period of rest, is a common characteristic symptom of several conditions and negatively impacts the quality of life of those affected. Fatigue is often a symptom of concern for people suffering from conditions such as fibromyalgia, chronic fatigue syndrome, cancer, and multiple sclerosis. Vitamins and minerals, playing essential roles in a variety of basic metabolic pathways that support fundamental cellular functions, may be important in mitigating physical and mental fatigue.

vitamin supplementation fatigue fatigue symptoms nutrient therapy

1. Clinical Populations

1.1. Vitamins and Minerals

Several studies have suggested the effects of oral supplementation with vitamins and minerals on fatigue amongst individuals suffering from different medical conditions [1]. Fatigue is the most common symptom of Multiple Sclerosis (MS), affecting up to 90% of those with MS, and is often reported as the first symptom noted by patients prior to diagnosis [2]. Moreover, fatigue is suggested to be more severe and disabling amongst MS patients than in healthy controls and others with chronic illness [2]. The administration of thiamine in MS patients for the management of fatigue has been investigated by Sevim et al. [3]. Daily oral administration of 400 mg sulbutiamine, a synthetic compound which constitutes two thiamine molecules, for two months was found to be effective in treating fatigue in MS. However, the effect was only observed in patients who were on disease modifying treatment, but not on those who were not [3]. Moreover, the effect of Alfacalcidol (1 a-hydroxycholecalciferol), a synthetic analogue of vitamin D, on MS-related fatigue has been investigated [4]. Intervention group received vitamin D3 alfacalcidol (1 µg or 40 IU) daily. Alfacalcidol lowered the mean Fatigue Impact Scale (FIS) score as compared with placebo and improved quality of life in patients with MS [4]. Moreover, Bager et al. has demonstrated the significant beneficial effect of high-dose oral thiamine (600–1800 mg/d) on chronic fatigue in patients with inflammatory bowel disease (IBD), following 4 weeks of treatment [5].

Vitamin D administration has been also reported to be associated with improvement of fatigue in various populations. Weekly administration of 50,000 IU oral cholecalciferol in patients with juvenile-onset systemic lupus erythematosus (SLE) improved many aspects of fatigue, including measures of ‘fatigue easily’, ‘fatigue during exercise’, ‘fatigue to medium efforts’, and ‘fatigue considered a problem’ [6]. Furthermore, oxidative stress is

thought to underlie fatigue, with serum markers of oxidative stress being associated with symptoms of CFS [7]. Since Vitamin C is a well-known antioxidant, vitamin C treatment for the management of fatigue symptoms has been investigated. Namely, in obese adults on a weight loss program with exercise, 500mg/day of oral vitamin C for four weeks was reported to be better than placebo in reducing the rate of perceived exertion and lowering fatigue scores [7]. The majority of studies, however, have investigated the effects of intravenous vitamin C on fatigue, which is furthered elaborated in Section 5.

1.2. Co-Enzymes

CoQ10 and NADH, common dietary supplements with purported cardioprotective effects, have been shown to significantly relieve fatigue symptoms [8]. Emerging data suggest that CFS and fibromyalgia are associated with deficiencies of CoQ10 and NADH, both of which play a pivotal role in mitochondrial ATP production and cellular metabolism homeostasis [8]. While mitochondrial failure decreases the rate of ATP synthesis which is the main agent of energy production in CFS, CoQ10 and NADH enhance cellular ATP production via mitochondrial oxidative phosphorylation [8]. Accordingly, in a study by Castro-Marrero et al., a clinical improvement in fatigue symptoms was demonstrated following initiation of oral NADH or CoQ10 supplementation in patients with CFS [9]. Thus, CoQ10 (200 mg/day) plus NADH (20 mg/day) administration is potentially a safe therapeutic approach for minimizing perceived cognitive fatigue and enhancing the health-related quality of life of individuals with ME/CFS [10]. Moreover, administration of NADH has been shown to be effective in the management of CFS symptoms [11]. In a study by Forsyth et al. [12], 10 mg of NADH was administered in CFS patients for a 4-week period. In this pilot study NADH was suggested as a valuable adjunctive therapy in the management of CFS [12]. However, it should be noted that another RCT study on the effects of 150 mg/day CoQ10 treatment in patients with CSF for two months failed to reveal any significant improvements ($p > 0.05$) in fatigue symptoms [13].

Oxidative stress and mitochondrial dysfunction have been found to play an important role in the pathogenesis of FM [14]. Furthermore, antioxidant proteins including catalase and superoxide dismutase (SOD) have been found to be diminished in FM [14]. While CoQ10 plays an important role in mitochondrial ATP production and cellular metabolism, fibromyalgia has been described to be linked with CoQ10 deficiency [14]. Accordingly, Miyamae et al. demonstrated that Ubiquinol-10 treatment in patients with juvenile FM and CoQ10 deficiency improved chronic fatigue scores as measured by the CFQ 11 [15]. Therefore, CoQ10 administration may cause remarkable improvements in FM patients. Cordero et al. investigated the efficacy of CoQ10 treatment (300 mg/day) on clinical and molecular parameters in fibromyalgia [16]. Forty days of CoQ10 administration resulted in significant reductions in pain, fatigue, and morning tiredness subscales of FIQ. Additionally, gene expression of IL-6, IL-8, and TNF was significantly reduced [16]. A higher dose of oral CoQ10, administered at 200 mg twice a day for three months, also seemed to statistically relieve fatigue symptoms in FM patients by approximately 22% [17].

Ultimately, while MS is a chronic inflammatory disorder accompanied by fatigue and depression [18], CoQ10 has neuroprotective and antioxidant properties, and hence decreases pro-inflammatory cytokines and protects the brain cells and neurons against central neurotoxic damages [19]. Therefore, the effect of CoQ10 administration on fatigue in patients with MS has been investigated [20]. The study reported a greater reduction in fatigue on the

fatigue severity scale in the CoQ10 group (500 mg/day for 12 weeks) than the placebo group [20]. Overall, CoQ10 supplementation has been investigated for the improvement of fatigue in various medical conditions. Three-month administration of 60 mg/day of CoQ10 in patients with end-stage heart failure awaiting heart transplantation caused a significant reduction in fatigue during activities of daily living, in addition to significant improvements in nocturia and dyspnoea [21]. Furthermore, in an RCT study by Peel et al., the efficacy of CoQ10 (100 mg/day for 2 moths) in alleviating fatigue symptoms in late-onset sequelae of poliomyelitis was investigated [22]. The results of the study, however, did not indicate any statistically significant ($p > 0.05$) reduction in fatigue [22]. Similarly, Lesser et al. did not support the efficacy of CoQ10 administration (300 mg/day for three months) in fatigue reduction in newly diagnosed patients with breast cancer [23]. Therefore, there is a need for further research on the effect of CoQ10 on fatigue symptoms amongst different populations and employing different doses and treatment durations.

1.3. Amino Acids

Carnitine, derived from the methylation of the amino acid lysine, plays an important role in the metabolism of fatty acids as the control of fatty acid oxidation is vested in the carnitine palmitoyltransferase system [24]. Moreover, skeletal and cardiac muscles, expressing carnitine palmitoyltransferase I (CPT I), use fatty acids as their primary source of energy. Therefore, in general, carnitine deficiency is associated with low energy levels, muscle weakness and general fatigue [24]. Cancer-related fatigue, characterized by a persistent sense of severe physical and psychological exhaustion related to cancer or its treatment, is amongst the most common symptoms in cancer patients [25]. Branched-chain amino acids have been suggested to reduce central fatigue [25]. Accordingly, Iwase et al. investigated the efficacy of a supplement containing branched-chain amino acids (2500 mg), CoQ10 (30 mg), and L-carnitine (50 mg) in the management of fatigue in breast cancer patients [26]. The significant reduction in fatigue scores suggested that the investigated intervention may be useful in controlling moderate-to-severe cancer-related fatigue [26]. However, Hershman et al. reported that in breast cancer patients undergoing adjuvant taxane-based chemotherapy, 3 g/day of oral L-carnitine for 24 weeks did not result in any significant changes in fatigue measures [27]. Another important finding of the study is that the results of the trial suggested a detrimental effect of the ALC intervention on chemotherapy-induced peripheral neuropathy (CIPN) [27]. Clearly, the use of nutritional supplements should be discouraged when there is evidence of adverse effects on any of the symptoms of the condition. Proven efficacy on different aspects of the condition should be available before any administration to avoid any potential harm. Nevertheless, chemotherapy medications including Ifosfamide and cisplatin cause urinary loss of carnitine; hence, carnitine treatment has been suggested for restoration of the carnitine pool and improving the chemotherapy-induced fatigue. Namely, administration of 4 g oral levocarnitine daily for 7 days was shown to ameliorate chemotherapy-induced fatigue in cancer patients [28]. Gramignano et al. also demonstrated that administration of 6 g/day of L-carnitine in cancer patients, significantly improved fatigue scores [29]. Altogether, there is a need for further studies investigating the effects of L-carnitine administration in patients with cancer and undergoing different treatments to ensure effective and safe administration of L-carnitine in this population.

L-carnitine administration has been investigated for the management of fatigue-related symptoms in several different conditions. Fatigue-related symptoms in hypothyroid patients have been suggested to be related to the relative deficiency of carnitine in these patients. Thyroid hormone plays an essential role in carnitine-dependent

fatty acid import and oxidation and decreased carnitine levels in hypothyroidism may be explained by decreased biosynthesis of carnitine [30]. Therefore, An et al. investigated the effects of L-carnitine treatment on fatigue-related symptoms in hypothyroid patients [30]. It was demonstrated that administration of L-carnitine (990 mg L-carnitine twice daily) in hypothyroid patients significantly improved physical fatigue score (PFS) and mental fatigue score (MFS) in patients younger than 50 years and those with free T3 ≥ 4.0 pg/mL [30]. Furthermore, levocarnitine tartrate administration (1000 mg daily for 12 weeks) has been found to significantly improve muscle weakness and fatigue in children with neurofibromatosis type 1 (NF1) [31].

Lastly, S-adenosylmethionine (SAM) is a methyl donor with a critical role in many metabolic processes. SAMe exerts anti-inflammatory, antidepressant, and analgesic effects, and is suggested to have tolerability equal to or better than the non-steroidal anti- inflammatory drugs [32]. The efficacy of 800 mg orally administered SAM daily versus placebo for six weeks was investigated in FM patients [32]. SAM treatment resulted in significant improvements in FM patients with regards to fatigue, clinical disease activity, morning stiffness, pain, and mood symptoms [32].

2. Non-Clinical Populations

2.1. Vitamins and Minerals

Administration of vitamins and minerals has also been investigated in populations without any known medical condition. Zinc is an intracellular signalling molecule which plays a critical role in various physiological processes including cellular proliferation, DNA repair, anti-inflammatory responses, immune system regulation, adenosine triphosphate (ATP) functioning, and regulation of enzymatic and muscle function [33]. Furthermore, zinc is vital for the control of proliferation, differentiation, and programmed cell death [34]. Namely, chronic zinc deprivation is associated with accelerated proliferation of vascular smooth muscle cells, which, in combination with calcification, can aggravate the progression of atherosclerosis [35]. Serum zinc concentration also diminishes with aging, with about 35% to 45% of the elderly having zinc levels lower than the normal range [36]. Regarding supplementation, in a study conducted on 150 elderly subjects aged ≥60 years, daily administration of 30 mg of zinc for 70 days significantly reduced fatigue and increased serum zinc levels [37]. Moreover, in a randomized, double-blind, placebo-controlled trial, administration of 220 mg of zinc sulphate in women with premenstrual syndrome (PMS) from the 16th day of each menstrual cycle to the 2nd day of the next for 3 months, resulted in significant improvements in fatigue scores as well as other symptoms of PMS monitored using the premenstrual symptoms screening tool [38]. Moreover, this improvement tended to increase each month, potentially due to the gradual improvement of zinc status [38].

2.2. Co-Enzymes

Several studies have investigated the administration of CoQ10 for improvement of fatigue in non-clinical populations [39], where the efficacy of CoQ10 administration on physical fatigue was examined using physical workload trials. Administration of 100 or 150 mg/day ubiquinol-10, the reduced form of CoQ10, was investigated by

Mizuno et al. [39]. Subjective levels of fatigue sensation and sleepiness after cognitive tasks improved significantly in both groups compared with those in the placebo group. Additionally, the group supplemented with 150 mg/day of ubiquinol-10 showed significant improvements compared with the control group in parameters such as serum level of oxidative stress, subjective level of relaxation after task, sleepiness before and after task, as well as motivation for task [39]. Moreover, in a study by the same group, 300 mg, but not 100 mg of CoQ10 administration alleviated the recovery period and the subjective fatigue sensation measured on a visual analogue scale [40]. In another study on the effects of CoQ10 administration on exercise performance in soccer players, four weeks of 300 mg/day CoQ10 administration did not result in any significant changes in fatigue scores as well as weight and body fat percent [41]. However, VO_2 max and performance in soccer players were significantly improved [41]. Gokbel et al. also investigated the efficacy of supplementation with 100 mg/day of CoQ10 on performance during repeated bouts of supramaximal exercise in sedentary men [42]. During the study period, five Wingate tests (WTs) were performed at baseline and after CoQ10, or placebo administration. Although CoQ10 resulted in a significant increase in mean power during the WT5, the observed decreases in fatigue indexes following 100 mg CoQ10 administration did not differ from that seen with placebo administration [42].

Several studies also reported no significant reduction in fatigue outcomes following CoQ10 administration [43]. Namely, the results from a study on the effects of CoQ10 on fatigue in obese subjects failed to show any significant change in mean FSS score between the placebo and CoQ10 groups [43]. The results of this research might be affected by the small sample of size of the trial [43]. Nonetheless, further studies on a larger sample size are required since changes in subjective fatigue between groups were not significantly different, even though the fatigue level improved significantly in the CoQ10 group.

2.3. Amino Acids

L-carnitine may be effective in improving cognitive status and physical functions in the elderly. L-carnitine administration has been found to reduce both mental and physical fatigue in aged subjects [44]. Malaguarnera et al. demonstrated that L-carnitine administration in the elderly (2 g twice a day) resulted in significant improvements in physical and mental fatigue, severity of fatigue, functional status, cognitive functions, muscle pain and sleep disorders [45]. The effects of acetylcarnitine and propionylcarnitine on the symptoms of CFS have been compared. It has been suggested that while Acetylcarnitine had a significant effect on mental fatigue and propionylcarnitine on general fatigue, both treatments improved attention concentration. However, less improvement was found for the combined treatment [46]. L-carnitine was also compared to androgen in the treatment of male aging symptoms. Subjects were given testosterone undecanoate 160 mg/day or propionyl-L-carnitine 2 g/day plus acetyl-L-carnitine 2 g/day. Both treatments significantly diminished the fatigue scale score at 3 months, and showed significant results for treatment of male aging symptoms [47].

3. Nutrient Deficiencies

3.1. Vitamins and Minerals

Vitamin deficiency is prevalent and has been found to be associated with fatigue in different populations. Accordingly, several studies have investigated vitamin D administration for the management of fatigue in subjects with vitamin D deficiency or insufficiency (i.e., suboptimal levels which are not low enough to be classified as deficient). While normal vitamin D levels typically range from 30 to 100 ng/mL, insufficient vitamin D levels are defined by serum levels between 20 ng/mL and 29 ng/mL, and serum levels below 20 ng/mL are classified as vitamin D deficiency [6]. Roy et al. [48] reported that the prevalence of low vitamin D was 77.2% in patients who presented with fatigue. Normalization of vitamin D levels by ergocalciferol (Vitamin D2) therapy for five weeks resulted in significant improvement in fatigue scores ($p < 0.001$) in all five subscale categories of FAS questionnaire [48]. Similarly, Nowak et al. reported that vitamin D administration in individuals presenting fatigue and vitamin D deficiency significantly improved FAS scores, with the improvements correlating with the rise in 25(OH)D levels [49]. Han et al. also demonstrated that serum 25(OH)D levels were inversely and independently related to fatigue scores in kidney transplant recipients (KTRs) exhibiting vitamin D deficiency [50]. Moreover, it was indicated that while fatigue was found in 40.1% of KTRs, vitamin D3 administration significantly increased 25(OH)D levels and improved fatigue symptoms in these patients [50]. Furthermore, vitamin D administration has been investigated for the management of post-stroke fatigue in patients with primary acute ischemic stroke (AIS) and vitamin D deficiency [51]. The study reported significant reduction in FFS scores in the study group compared to the control group, at both one month ($t = -4.731$, $p < 0.01$) and three months ($t = -7.937$, $p < 0.01$) following vitamin D administration [51]. Lastly, 12 weeks of treatment with 50,000 IU vitamin D3 weekly in post-menopausal women with early-stage breast cancer exhibiting vitamin D deficiency or insufficiency was investigated [52]. However, the difference between the fatigue scores of subjects exhibiting 25OHD levels above the median (66 ng/mL) and those with 25OHD levels below the median were not statistically significant. Overall, vitamin D deficiency co-presents in many medical conditions in association with fatigue symptoms.

Additionally, it has been indicated that the fatigue and related manifestations concomitant with MS are associated with an intracellular mild thiamine deficiency [1]. Costantini et al. demonstrated that high-dose thiamine therapy (600–1500 mg/day orally or 100 mg/mL once a week parenterally) was effective in reversing fatigue in MS [1]. Interestingly, it was demonstrated that improvement in fatigue was observed within hours from the first parenteral administration or within 2–3 days following initiation of the oral therapy [1].

3.2. Amino Acids

As mentioned, carnitine deficiency can result in low energy levels, muscle weakness and general fatigue [24]. In cancer patients, carnitine deficiency is amongst the many metabolic disturbances that may contribute to fatigue. L-carnitine administration (1500 mg/day of levocarnitine per os) has been shown to improve general fatigue in cancer patients during chemotherapy [53]. A few studies by Cruciani et al. have explored administration of L-carnitine in cancer patients with L-carnitine deficiency [54]. In these studies, carnitine deficiency was defined as free carnitine < 35 mM/L for males or <25 mM/L for females, or an acyl-carnitine ratio (total carnitine minus free carnitine/free carnitine) > 0.4 [54]. Thereafter, cancer patients with carnitine deficiency were assigned to successive dose groups, starting at 250 mg/day and increasing in each group by 500 mg/day to a maximum dose target of 3000 mg/day [54]. The results showed a significant decrease in measures of fatigue (Brief Fatigue Inventory, BFI) with a dose-

response relationship for free-carnitine levels and fatigue (BFI) scores, suggesting that L-carnitine may be safely administered at doses up to 3000 mg/day [55]. However, a couple of investigations by Cruciani et al. failed to show any significant improvements in fatigue symptoms with L-carnitine treatment [56]. In the study investigating the effects of L-carnitine supplementation as a treatment for fatigue in patients with cancer, four weeks of 2 g/day of L-carnitine administration failed to improve fatigue in patients with invasive malignancies [56]. However, the reported results might be due to the dose and duration of L-carnitine administration employed in this research, which are different from those of some other studies showing positive outcomes. Furthermore, no significant improvement in fatigue symptoms was observed in terminally ill HIV/AIDS patients with carnitine deficiency and fatigue receiving 3 g/day of oral L-carnitine for 2 weeks [57]. It should be noted that this research might have been less representative due to several factors such as poor participant accrual, the excessive number of outcome measures, and effect size of the study [57].

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