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Review

Chronic fatigue syndrome (CFS): Suggestions for a nutritional treatment in the therapeutic approach

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Abstract

Chronic fatigue syndrome (CFS) is known as a multi-systemic and complex illness, which induces fatigue and long-term disability in educational, occupational, social, or personal activities. The diagnosis of this disease is difficult, due to lacking a proper and suited diagnostic laboratory test, besides to its multifaceted symptoms. Numerous factors, including environmental and immunological issues, and a large spectrum of CFS symptoms, have recently been reported. In this review, we focus on the nutritional intervention in CFS, discussing the many immunological, environmental, and nutritional aspects currently investigated about this disease. Changes in immunoglobulin levels, cytokine profiles and B- and T- cell phenotype and declined cytotoxicity of natural killer cells, are commonly reported features of immune dysregulation in CFS. Also, some nutrient deficiencies (vitamin C, vitamin B complex, sodium, magnesium, zinc, folic acid, L-carnitine, L-tryptophan, essential fatty acids, and coenzyme Q_{10}) appear to be important in the severity and

exacerbation of CFS symptoms. This review highlights a far-driven analysis of mineral and vitamin deficiencies among CFS patients.

Previous Next

Keywords

Chronic fatigue syndrome; Nutrients; Immunoglobulins; Cytokines; Lymphocyte transformation; Delayed hypersensitivity

1. Introduction

Chronic fatigue syndrome (CFS) is a distinctive syndrome characterized by prolonged fatigue in combination with typical symptoms such as muscle and joint pain, or headaches, tender lymph nodes, recurrent sore throat, significant problems with cognition and concentration, memory, and sleep, and deterioration after physical activity [[1], [2], [3], [4], [5], [6], [7], [8], [9], [10]] (Fig. 1). The CFS diagnosis is given only in disease states with a history of at least six months, and could only be identified after other fatigue etiologies have been excluded [11]. The syndrome often results in severe functional limitation. CFS may also be known as chronic fatigue immune dysfunction syndrome, postviral fatigue syndrome, myalgic encephalomyelitis (ME), or named by several other terms [12]. The prevalence of CFS varies from 0.4 to 2.5% in the general population of the USA and the UK [13]. CFS has its highest impact in females, rather than in males [14,15]. A possible reason is still far to be elucidated, although CFS etiopathogenesis may have genetic and epigenetic origins, [16] besides hormonal, viral and immune causes [17]. The kinship with the wide cohort of autoimmune diseases might shed light on the possible relationship between CFS and its higher frequency in female subjects [7,18]. Estrogens and estrogen receptors, particularly the ER-beta, are impaired and lowly expressed in subjects with CFS, a circumstance that can be particularly exacerbated in female individuals [19,20]. CFS prevalence is estimated to be 836,000 to 2.5 million in American people in 2015, according to the Institute of Medicine (IOM), although most of them have not been identified [21]. Many of CFS patients show anxiety and depression disorders [22] with prevalence rates of 42.2% and 33.3% respectively [23]. The social, cultural, anthropological and personal effects of CFS are enormous on human economy, and this condition is still poorly understood. The fatigue symptoms may aggravate with mental or physical activity, but they do not improve after resting periods. It has been demonstrated that CFS might be the result of a mix of factors, such as viral

infections (human herpesvirus-6, mouse leukemia viruses, and Epstein-Barr virus (EBV), intracellular bacteria, environmental factors, and immune system disabilities, hormonal imbalances in the pituitary glands, adrenal glands, or hypothalamus [7,24,25]. Herpesviruses have been longtime included as a causal factor of CFS etiology [24,26]. Particularly concerning EBV, the pathogenesis of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is caused by a viral infection, which elicits the formation of ectopic lymphoid aggregates [27]. The viral etiopathogenesis of CFS is a possible causative hypothesis, leading to immune disorders [28]. However, the autoimmune tenet, by which CFS is finally elucidated, is another hallmark in the pathway towards the comprehension of the pathology. What is emerging from medicine, is that clinical CFS is considered part of a spectrum of diseases including fibromyalgia, irritable bowel syndrome and perhaps some further autoimmune diseases, and thereby may be linked with autoimmune manifestations as well as exposure to drugs or vaccines [29,30]. Further suggestions come from investigating gut microbiota and its relationship with CFS [31]. A hypothesis has been forwarded regarding the presence in the gut microbiome of CFS patients of D-lactate producing bacteria, such as occurring in the D-lactate acidosis, for which synbiotics may be a possible treatment [32,33]. Probiotics may be considered a therapeutic possibility for CFS, as well as fibromyalgia [9,34]. However, as the impairment in the gut-brain axis includes microbiota, and intestinal immunity, several immune-targeted treatments of CFS have also been taken into consideration, such as B-cell clonal depletion and the use of humanized antibodies [[35], [36], [37]].

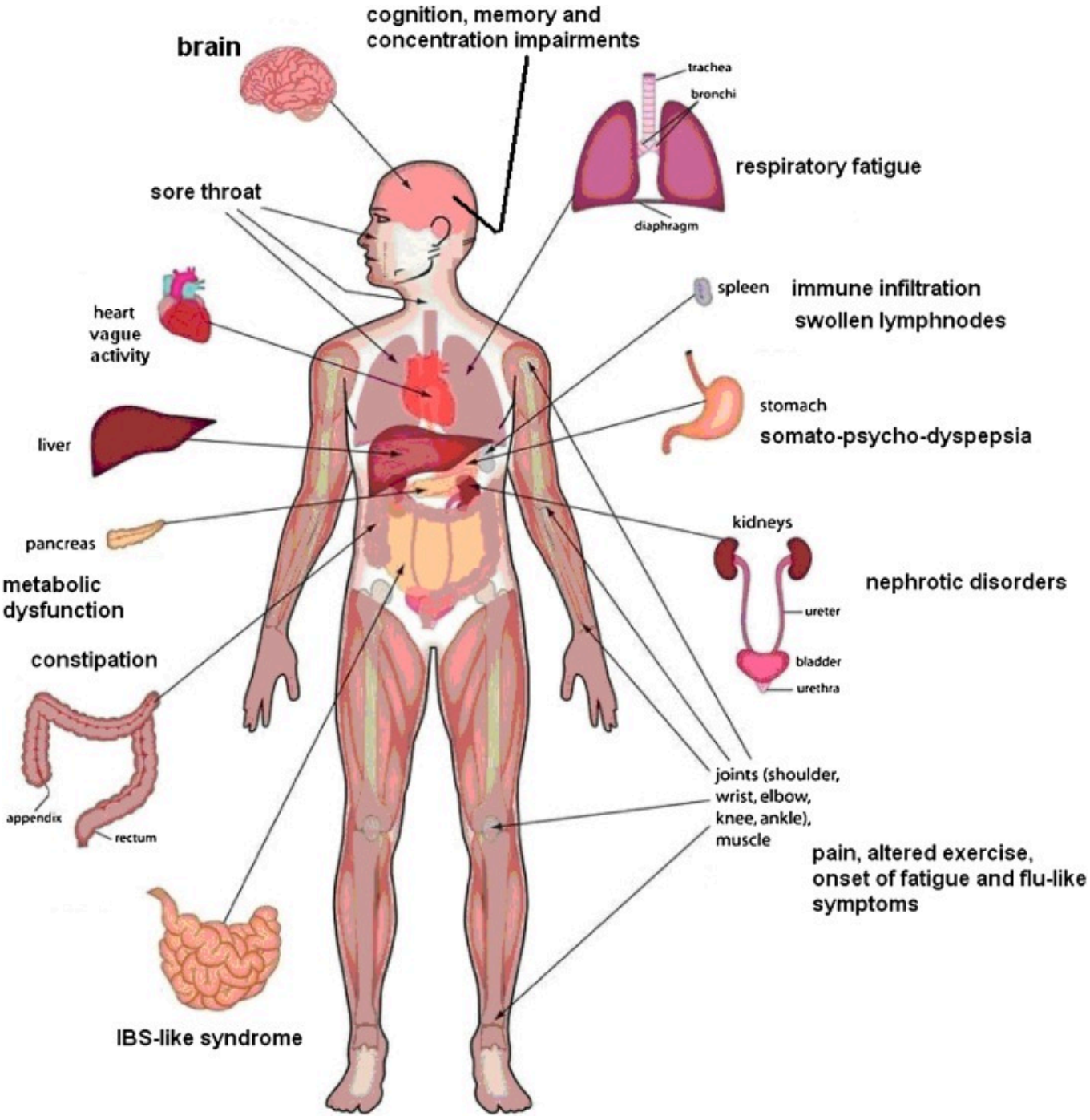

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Fig. 1. The involvement of human body organs in chronic fatigue syndrome.

Usually, CFS symptoms are associated with loss of memory, headaches, fatigue, enlarged and painful lymph nodes in the neck or armpits, unrefreshing sleep, cognitive dysfunction, sore throat, unexplained muscle or joint pain, and severe exhaustion over a 24-hour period after mental or physical exercise [38,39]. Although there are significant attempts worldwide to elucidate the onset of CFS, no single etiology has been reported for this syndrome. It is

thought that a variety of causes induces the development of CFS. Therefore, this review will try to highlight the current evidence related to CFS pathogenesis as related to nutrition, reliable biomarkers, nutritional interventions, as well as possible treatments, to reveal potential nutritional interference. In addition, this review aims to present numerous aspects of the syndrome that could be prone to successful intervention, such as fatigue or an impaired immune response to metals and viral infections.

2. A brief insight into the pathogenesis of chronic fatigue syndrome

The etiology of CFS is unknown; however, observations suggest that there may be at least two different etiological subgroups. One subgroup consists of patients with early, often undiagnosed Parkinson's disease [40] and may have further degenerative brain diseases [41], while the other subgroup appears to be composed of patients with various low-grade, but chronic infections or inflammations, including infections with herpesvirus-6, Epstein-Barr virus and various enteroviruses [42], [43], [44], [45], [46]. These infections could often be diagnosed serologically, when looked for; yet, even in cases where no specific infectious agent has been identified, it is likely to observe further signs strongly suggesting chronic viral infection, such as high concentrations of protein kinase R (PKR) [47], RNase L [47], [48], [49], 2–5 A synthetase [50] and elastase in leukocytes [47], while at the same time RNase L inhibitor may be downregulated. Furthermore, double-stranded RNA could induce the RNase L inhibitor (RLI) [50]. The pathway of 2–5 A synthetase/RNase L in patients with CFS shows to be deregulated (elastase and calpain initiate 83 kDa RNase L proteolysis, generating two major fragments with molecular masses of 37 and 30 kDa, respectively) and upregulated (*i.e.* an increased activity of the RNase L enzyme and elevated levels of bioactive 2–5 A synthetase) [51].

Moreover, the role of NK cells in CFS is of major importance [52]. During CFS, a dysregulation of protein kinase genes, causing NK cell dysfunction with a marked reduction in the NK cytotoxic activity, was observed [52,53]. The immunological landscape of CFS is particularly complex [54]. A hypothesis about the NK-functional impairment in CFS regards the activity of the Transient Receptor Potential Melastatin 3 (TRPM3) cation channels in NK cells, channels that showed a significant reduction in amplitude of the TRPM3 current after pregnenolone sulfate stimulation in isolated NK cells from CFS patients [55].

PKR is a component of the innate immunity antiviral pathway [55,56]. It is activated upon binding to double-stranded RNA (dsRNA) to undergo dimerization and autophosphorylation [56]. Its activations in the bulk of cellular mechanisms, such as cellular and viral stress responses, is modulated through the phosphorylation of the translation initiation factor

eIF2α [57]. PKR function needs some minimal requirements such as autophosphorylation at the residue T446 in a flexible loop, named the activation loop, and homodimerization of its kinase and RNA-binding domains [57]. Chronic activation of signaling pathways associated with innate antiviral defense is likely to be central in the pathogenesis of CFS, since many of the antiviral effector molecules (as well-known defense weapons), which are upregulated, are not specific enough to attack only viral nucleic acids or protein, without harming host cell macromolecules and functions (by inhibition of synthesis or enhanced degradation of the host cell macromolecule), as well.

While PKR activation in leukocytes in many patients with CFS must be regarded as the evidence strongly suggestive of an infectious etiology, some caution might, nevertheless, be warranted, since PKR has also been reported to be activated by toxic oligomers of the Alzheimer protein β-amyloid [54]. Therefore, PKR may play an important role in neurological disorders such as the Alzheimer's disease, even without any viral cause. However, simultaneous detection of increased levels of pro-inflammatory cytokines, such as TNF-*alpha* and IL-1, in patients [58,59] is indicative of an infectious or inflammatory etiology. Increased neopterin levels in blood plasma also indicate an ongoing inflammation [58,59].

3. Chronic fatigue syndrome and toxic metals

Studies have shown that delayed-type hypersensitivity (type 4 allergy) to nickel (Ni) and Hg is more frequent in patients with CFS, compared to healthy controls [[60], [61], [62]]. It has also been reported that CFS patients' symptoms could be improved after the removal of dental amalgam [[63], [64], [65]]. Past reports from Stejskal et al. investigated the role of dental amalgam removal in 111 patients with symptoms resembling CFS and metal hypersensitivity [63]. MELISA, the optimized lymphocyte transformation test, was used to test for the presence of metal allergy. When comparing 116 healthy subjects, a CSF-like syndrome has been reported, using metal-specific lymphocytes in the blood of a significant number of patients [63,64]. Nickel was reported as one of the most frequent sensitizers, followed by inorganic Hg, Ag, phenyl mercury, cadmium (Cd), and palladium (Pd) [64]. The reactivity of lymphocytes to metals declined after dental metal removal, and 83 patients (76%) showed long-term health improvement, 24 patients (22%) showed unchanged health and two of them (2%) showed worsening of symptoms [64]. Although metal-induced inflammation is involved in the pathogenesis of CFS, important observations are suggesting that chronic viral infections may be an important part of the etiopathogenesis at least in a large subgroup of patients [46,[65], [66], [67]]. Presumably, the many factors that may contribute to suppression of the parts of the immune system that are important for fighting

viruses will enhance the risk of chronic or long-lasting infection, resulting in the development of CFS. Potentially important contributory mechanisms in CFS, may be the reduced leukocyte growth rates and the reduced expression of high-affinity and/or intermediate-affinity receptors for interleukin-2 (IL-2) on leukocytes, resulting from poor functional Se status [66,68,69], due to the combined effect of suboptimal Se intake and a high total content of Se-antagonistic toxic metals [70,71]. Enhanced expression of the immunosuppressive cytokine TGF-β may result from toxic metal exposure, because of the induction by the lipid peroxidation product 4-hydroxynonenal [72], an induction which is also triggered by poor Se status [73,74].

4. Nutrition and nutraceutical supplementation. Insights into the role of selenium in the chronic fatigue syndrome

Sub-optimal Se intake or poor functional Se status, due to too much Se-antagonistic toxic metals, is expected to lead to an enhanced synthesis of prostaglandin E_2 (PGE_2) [75]. Oxidative activation of signaling pathways causing enhanced expression of cyclooxygenase-2 (COX-2) in individuals with poor Se status and a high ratio of *omega-6* to *omega-3* polyunsaturated fatty acids (PUFAs) in the diet, will also cause an increased prostaglandin synthesis [75,76]. For example, the prostaglandin PGE_2 is an important suppressor of leukocyte types that are important for fighting viral infections. At the same time, PGE_2 is one of the important signal substances, skewing the phenotype of macrophages from being antiviral and antitumor soldiers to become immunosuppressive M2 macrophages [77]. This is an important snowball effect of deficient Se status and high intake of *omega-6* PUFAs since PGE_2 increases the expression of non-protective enzymes in leukocytes [[78], [79], [80]].

5. Bacterial and viral co-infections in CFS as a leading cause of microbiota impairment

It is a plausible working hypothesis that CFS may be a disease perpetuating itself because of a number of interlocking vicious circles, leading to immunosuppression, due to the deleterious effect of infection *per se* or other chronic inflammatory conditions [[81], [82], [83]]. Gut microbiota is expected to exert a leading role in this sense [84]. The resulting inflammatory reactions may be self-perpetuating, which causes enhancement of oxidative and nitrative stress [2,59], as well as enhanced degradation of several nutrients. In turn, this can lead to persistence of various infections at a moderate level of activity, which is not acutely life-threatening but can lead to very remarkable impairment of the patient's quality

of life. If this hypothesis is correct, treatment should be directed at trying to break as many as possible of the vicious circles concerned through a multifactorial intervention.

In the gastrointestinal tract, it is conceivable that inhibition of a nucleolar protein might cause inhibition of the growth of enterocyte and colonocyte progenitor cells, as well as various forms of disturbance of immunological functions, which may play a role not only in chronic infections but also in allergic and autoimmune disorders [85]. Moreover, it is also conceivable that inhibition of nucleolar function might cause reduced production of various secreted proteins that are needed for the normal function of the gastrointestinal tract, and perhaps enhanced leakiness of the mucosal epithelium. Also, it has been revealed that chronic infections are the most common feature of illness in CFS patients [85]. Numerous studies in American and European CFS patients reported that the most common of bacterial infections are due to mycoplasma [85,86]. For example, a study of 261 CFS patients showed that 68.6% of Belgian patients have one or more species of mycoplasma in their blood [87]. Furthermore, it has been reported that North American CFS patients had *M. hominidis* as the most common species, revealing the differences in exposures and demography between Belgian and North American CFS patients. Another study with 200 CFS patients confirmed a high prevalence (overall 52%) of mycoplasma infections, along with Chlamydia *pneumoniae* and human herpesvirus-6 [86,88]. Also, CFS patients show evidence of Brucella spp. [86,89,90]. Certain types of infections in CFS patients are also commonly reported as human herpesvirus-6 (HHV-6), mouse leukemia viruses and Epstein-Barr virus, *Chlamydia*, and Borrelia species [88].

6. Nutrition byproducts. Chronic fatigue syndrome and oxidative stress

Many CFS patients show nitrosative and oxidative stress, and a chronically activated innate immune system [2,91]. Recent studies have demonstrated that the generation of free radicals could be involved in CFS etiology [1,3,91]. Fatigue symptoms could be related to the loss in the effectiveness of the electron transport chain and declined mitochondrial function. Oxidative mitochondrial damage, particularly from Reactive Oxygen Species (ROS), induces damage to mitochondrial membrane lipids, which results in rapid loss of mitochondrial function, although it causes the peroxidation of proteins and DNA as well as the cellular mitochondrial lipids [92]. In other words, because of the formation of excess free radicals, oxidative stress could be involved in the CFS pathology, as well as being associated with symptomatic presentation [93]. Chronically activated immune-inflammatory responses and nitrosative and oxidative stress in CFS patients, induce brain disorders such as brain hypoperfusion/hypometabolism, neuroinflammation, DNA damage, mitochondrial dysfunctions, secondary autoimmune responses directed against disrupted

proteins and lipid membrane components, and dysfunctional intracellular signaling pathways [2,3,93]. Furthermore, Morris and his colleagues reported that hypofunction of the hypothalamic-pituitary-adrenal axis in CFS patients is known as a consequence of nitrosative and oxidative pathways, and stimulated immune-inflammatory responses [1]. The explanations of this mechanism could be attributed to the elevated levels of tumor necrosis factor-α, increased levels of nitric oxide, regulatory T cell responses with increased levels of transforming growth factor-β and interleukin-10, and viral/bacterial-mediated pathways [1]. Oxidative stress and energy metabolism have been elucidated as a dysfunction in the metabolic pathways of CFS patients [94]. Moreover, the response of CFS patients to accumulative exercise is related with accentuated oxidative stress, as well as with noticeable changes in the muscle membrane dysfunction that induce post-exercise malaise and muscle pain reported by CFS patients [95,96]. Finally, IgM-associated immune responses, directed against disrupted lipid membrane components and proteins, could be induced by nitrosative or oxidative stress in CFS patients [97].

7. Chronic fatigue syndrome and reliable biomarkers in the nutrition therapy

Anti-oxidative and pro-oxidant stress activity could be applied as markers for CFS patients [11,98]. Moreover, the 8-iso-prostaglandin-F2α-isoprostane contents could be used as a plasma biomarker of nutrient-derived oxidative stress in CFS patients [99]. A significant decrease in the cytotoxic activity of natural killer (NK) cells, as detailed in the introduction, is a persistent finding in CFS patients compared with healthy controls [100,101]. Furthermore, a notable increase in $CD19^{+}IgM^{+}$ B cells and $CD20^{+}CD5^{+}$ B cells has also been described in CFS [102]. Another study reported that elevated CD38 and human leukocyte antigen (HLA)-DR expression on $CD8^{+}$ T cells could be used as markers of CFS [103]. The relevance of biomarkers with health-related quality of life and history of stressors in CFS patients revealed that severe changes of the redox status, muscle excitability, and the level of CD26-expression, are related to an important impairment of the quality-of-life [104]. Microarray analysis of 34 microRNAs in the peripheral blood mononuclear cells (PBMC) from CFS patients showed that hsa-miR-99b, hsa-miR-126, hsa-miR-330, and hsa-miR-30c are potential diagnostic biomarkers in NK cells of CFS patients [105]. All four biomarkers may differentiate CFS patients from healthy controls and suggests a changed activation of the NK cell pathway in CFS, for the decreased effector function seen in CFS. On the other hand, activin B, which is a protein member of the Transforming Growth Factor-β (TGF-β) family, is reported as a new biomarker for CFS patients. The evaluation of the activin levels

and follistatin levels will be useful in separating CFS from other fatigue-related disorders [106].

8. Chronic fatigue syndrome and nutritional intervention

The cellular energy systems of mitochondria appear to contribute to the complex pattern of symptoms in CFS. It has been reported that cellular mitochondrial damage can spoil the cell's abilities to produce high-energy molecules, including NADH and ATP. This occurs naturally during chronic illness, mainly because of damaged mitochondrial components with impaired function [92]. Over the last years, there has been a significant increase in the quality of evidence-based nutritional intervention for CFS. A brief summary of the suggested nutritional interventions in CFS is summarized in Table 1.

Table 1. Nutritional supplements suggested in chronic fatigue syndrome; an alternative recommendation can be found in reference [117].

Nutrient	Dose	Number of Patients	Reference
Vitamin B12	1–10 mg/week (IM)	38	[108]
Folic acid	1–5 mg/day (oral)	38	[108]
Supradyn®	1/day (oral)	38	[110]
NADH + coenzyme Q_{10}	20 mg/day + 200 mg/day (oral)	73	[89]
D-ribose	3 × 5 mg/day	41	[116]

Numerous reviews reported that some nutritional deficiencies could be involved as etiologic agents for CFS. These include deficiencies of vitamin C, vitamin B complex, sodium, magnesium, zinc, folic acid, L-carnitine, L-tryptophan, essential fatty acids, and coenzyme Q_{10} [107]. For example, a dose-response association and long-lasting effects of B12/folic acid provide a proper positive reaction in the examined CFS patients [108]. The low content of serum vitamin E during the remission and exacerbation phase of CFS patients revealed that high oxidative stress could be contributing to the CFS pathogenesis, and may be directly related to the severity of the symptoms of CFS patients, indicating that antioxidant supplementation could alleviate muscle symptoms in this syndrome [109]. Moreover, Maric and his colleagues revealed that multivitamin-mineral supplements could be a safe and easy approach to alleviate the CFS symptoms and improve quality of life [110].

Adequate lipid replacement and antioxidant therapy as nutritional supplements, could control oxidative membrane damage and restore cellular membrane and mitochondrial functions, through the delivery of undamaged lipids and antioxidants to oxidized lipids of cellular organelles, to remove damaged lipids by lipid replacement [111]. Recent clinical trials using CFS patients have reported the benefit of antioxidants and lipids to reduce moderate to severe CFS symptoms. Another study showed that a combination of glycophospholipid-antioxidant-vitamin significantly decreases the symptoms of fatigue within one week [112]. Overall, the various forms of nutritional intervention highlight mixed outcomes in terms of efficacy.

All results concerning efficacy might be evaluated along with the inadequate approaches in studies. Nutritional interventions have reported potential results regarding graded exercise therapy and behavioral therapy. Further evaluation of nutritional treatment is hotly demanded through approaches to obtain standardized results.

9. Clinical evidence

Numerous clinical studies concerning CFS have been published, but drawing final conclusions is extremely difficult, due to the diverse nature of the syndrome. The lack of a straightforward definition, as well as of clear-cut criteria, makes it difficult to compare studies. In result, there exists significant overlap with other diseases, causing an important bias in many clinical trials. Moreover, nutritional intervention has only recently come to be appreciated as part of a therapeutic approach, limiting the amount of evidence. Most existing trials are observational, and those that are interventional, do not always display high quality, with the number of actual RCT's, although the gold standard, being rather limited. Another problem is the nature of using nutritional supplementation, which can be centered around a single nutrient, but also in the form of combinations in a cocktail, making analysis and drawing conclusions difficult. Nevertheless, some rather interesting trends, also from systematic reviews with or without meta-analysis, can be observed at this time.

A study examining alternative treatments, found some hints towards a positive effect on CFS, making use of magnesium, L-carnitine, and S-adenosylmethionine as supplements in CFS patients [113]. However, it should be highlighted that most trials are of poor quality, using different methods (including a dosage of nutrients), lacking documentation of dietary intake, showing only a short follow-up, examining only a small number of patients, using a heterogeneous population, and lacking sound clinical endpoints. Despite these shortcomings, the majority of trials examined, showed positive results, warranting confirmatory trials.

A more recent evaluation could not demonstrate an effect on CFS outcome, but most trials did have an effect on symptoms, typically fatigue, using nicotinamide adenine dinucleotide hydride (NADH), probiotics, chocolate, and coenzyme Q_{10} [114]. As nutritional trials are difficult to perform properly, overall quality remains poor, owing to the same problems encountered as mentioned above. Again, nutritional supplements are hinted to alleviate at least some of the problems encountered with CFS.

Eventually, a meta-analysis was recently performed, not able to confirm that vitamin and mineral deficiencies altogether play a major role in CFS, but with some doubt remaining on vitamin E deficiency [115]. This analysis also could not find any benefit from nutritional intervention, although only a very limited number of interventional trials were examined here.

Finally, another systematic review suggested a positive effect of nutritional supplements again, such as D-ribose, albeit only on symptoms, with special regard to supplementation of *omega-3* fatty acids, whose blood levels could also be linked to relief of symptoms [116]. Again, all the previously mentioned shortcomings continue to exist, and no final conclusion can be drawn at this point.

10. Conclusion

Despite the huge amount of hypotheses, the most frequent suggestion is that an infectious etiology should be regarded as being plausible for the etiology of CFS. However, possible further causes related to the gut/brain axis and the microbiota-related immune disorders, including autoimmunity, are possible suggestions. The numerous investigated classifications of CFS patients, with regard to symptomatic patterns and severity, could be useful to anticipate effectiveness or therapeutic prognosis. Many insights are to be elucidated, anyway. A meta-analysis with 27 studies concludes that there are still few data to provide a promising hypothesis for the effective role of mineral and vitamin supplementation in the CFS pathophysiology and therapy. Current studies on minerals and vitamins in CFS patients need large population-based and age-matched prospective research, as well as well-observed interventional studies in CFS patients, to achieve more awareness in the efficacy of minerals and vitamins in the CFS pathophysiology. According to this analysis, vitamin A and vitamin E are promising vitamins that need further examination.

Further analysis of CFS patients can be earned by applying diagnostic criteria according to systematic evaluation. In addition, future investigations need to evaluate whether phenotypes of CFS predict the outcome of treatment. On the other hand, anxiety and

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