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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.

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 [1–10] (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,

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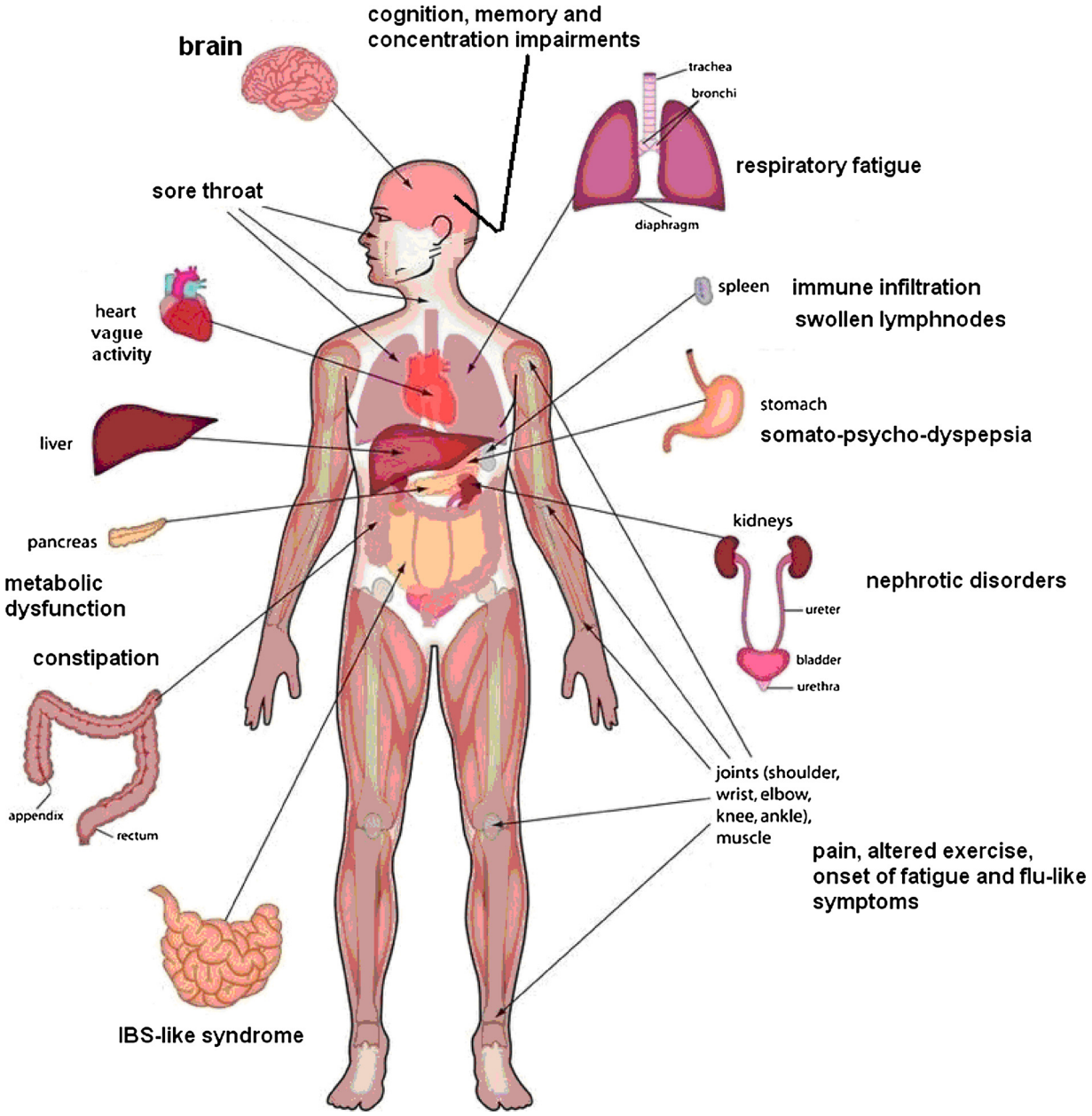

Fig. 1. The involvement of human body organs in chronic fatigue syndrome.

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 [35–37].

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 [42–46]. 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 [47–49], 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 [60–62]. It has also been reported that CFS patients' symptoms could be improved after the removal of dental amalgam [63–65]. 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 [46,65–67]. 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 [78–80].

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 [81–83]. 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.

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

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]

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 depression of CFS patients warrant further studies to explore a better vision of how these features could influence symptomatic and interventional management.

References

[1] G. Morris, G. Anderson, M. Maes, Hypothalamic-pituitary-adrenal hypofunction in myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) as a consequence of activated immune-inflammatory and oxidative and nitrosative pathways, Mol. Neurobiol. 5 (2017) 6806–6819.

[2] G. Morris, M. Maes, Oxidative and nitrosative stress and immune-inflammatory pathways in patients with myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS), Curr. Neuropharmacol. 12 (2014) 168–185.

[3] G. Morris, B. Stubbs, C.A. Köhler, K. Walder, A. Slyepchenko, M. Berk, A.F. Carvalho, The putative role of oxidative stress and inflammation in the pathophysiology of sleep dysfunction across neuropsychiatric disorders: focus on chronic fatigue syndrome, bipolar disorder and multiple sclerosis, Sleep Med. Rev. 41 (2018) 255–266.

[4] T.E. Lacourt, E.G. Vichaya, G.S. Chiu, R. Dantzer, C.J. Heijnen, The high costs of low-grade inflammation: persistent fatigue as a consequence of reduced cellular-energy availability and non-adaptive energy expenditure, Front. Behav. Neurosci. 12 (2018).

[5] T. Teodoro, M.J. Edwards, J.D. Isaacs, A unifying theory for cognitive abnormalities in functional neurological disorders, fibromyalgia and chronic fatigue syndrome: systematic review, J. Neurol. Neurosurg. J. Neurol. Neurosurg. Psychiatry (2018), https://doi.org/10.1136/jnnp-2017-317823.

[6] C. Tomas, J. Newton, Metabolic abnormalities in chronic fatigue syndrome/myalgic encephalomyelitis: a mini-review, Biochem. Soc. Trans. 46 (2018) 547–553, https://doi.org/10.1042/BST20170503.

[7] F. Sotzny, J. Blanco, E. Capelli, J. Castro-Marrero, S. Steiner, M. Murovska, C. Scheibenbogen, Myalgic encephalomyelitis/chronic fatigue syndrome–evidence for an autoimmune disease, Autoimmun. Rev. 17 (2018) 601–609, https://doi.org/10.1016/j.autrev.2018.01.009.

[8] F. Newberry, S.-Y. Hsieh, T. Wileman, S.R. Carding, Does the microbiome and virome contribute to myalgic encephalomyelitis/chronic fatigue syndrome? Clin. Sci. 132 (2018) 523–542.

[9] M. Corbitt, N. Campagnolo, D. Staines, S. Marshall-Gradisnik, A systematic review of probiotic interventions for gastrointestinal symptoms and irritable bowel syndrome in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), Probiotics Antimicrob. Proteins 10 (2018) 466–477, https://doi.org/10.1007/s12602-018-9397-8.

[10] J.A. Monro, B.K. Puri, A molecular neurobiological approach to understanding the aetiology of chronic fatigue syndrome (myalgic encephalomyelitis or systemic exertion intolerance disease) with treatment implications, Mol. Neurobiol. 55 (2018) 7377–7388.

[11] K. Fukuda, S.E. Straus, I. Hickie, M.C. Sharpe, J.G. Dobbins, A. Komaroff, The chronic fatigue syndrome: a comprehensive approach to its definition and study, Ann. Intern. Med. 121 (1994) 953–959.

[12] S. Baos, A. Brigden, E. Anderson, W. Hollingworth, S. Price, N. Mills, L. Beasant, D. Gaunt, K. Garfield, C. Metcalfe, Investigating the effectiveness and cost-effectiveness of FITNET-NHS (Fatigue In Teenagers on the interNET in the NHS)

compared to activity management to treat paediatric chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME): protocol for a randomised controlled trial, Trials 19 (2018) 136.
[13] B. Van Houdenhove, P. Luyten, Customizing treatment of chronic fatigue syndrome and fibromyalgia: the role of perpetuating factors, Psychosomatics 49 (2008) 470–477.
[14] M. Faro, N. Sàez-Francás, J. Castro-Marrero, L. Aliste, T.F. de Sevilla, J. Alegre, Gender differences in chronic fatigue syndrome, Reumatol. Clin. 12 (2016) 72–77, https://doi.org/10.1016/j.reuma.2015.05.007.
[15] E. Iacob, A.R. Light, G.W. Donaldson, A. Okifuji, R.W. Hughen, A.T. White, K.C. Light, Gene expression factor analysis to differentiate pathways linked to fibromyalgia, chronic fatigue syndrome, and depression in a diverse patient sample, Arthritis Care Res. (Hoboken) 68 (2016) 132–140.
[16] W.C. de Vega, S.D. Vernon, P.O. McGowan, DNA methylation modifications associated with chronic fatigue syndrome, PLoS One 9 (2014) e104757, , https://doi.org/10.1371/journal.pone.0104757.
[17] J. Blomberg, C.-G. Gottfries, A. Elfaitouri, M. Rizwan, A. Rosén, Infection elicited autoimmunity and myalgic encephalomyelitis/chronic fatigue syndrome: an explanatory model, Front. Immunol. 9 (2018) 229.
[18] N. Sinaii, S.D. Cleary, M. Ballweg, L.K. Nieman, P. Stratton, High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis, Hum. Reprod. 17 (2002) 2715–2724.
[19] J.-D. De Korwin, L. Chiche, I. Banovic, A. Ghali, S. Delliaux, F.-J. Authier, G. Cozon, P.-Y. Hatron, I. Fornasieri, F. Morinet, Chronic fatigue syndrome: a new disorder? (in French), Rev. Med. Interne 37 (2016) 811–819.
[20] H. Gräns, M. Nilsson, K. Dahlman-Wright, B. Evengård, Reduced levels of oestrogen receptor β mRNA in Swedish patients with chronic fatigue syndrome, J. Clin. Pathol. 60 (2007) 195–198.
[21] E.W. Clayton, Beyond myalgic encephalomyelitis/chronic fatigue syndrome: an IOM report on redefining an illness, JAMA 313 (2015) 1101–1102.
[22] K.A. Janssens, W.L. Zijlema, M.L. Joustra, J.G. Rosmalen, Mood and anxiety disorders in chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome: results from the LifeLines cohort study, Psychosom. Med. 77 (2015) 449–457.
[23] J. Daniels, A. Brigden, A. Kacorova, Anxiety and depression in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): examining the incidence of health anxiety in CFS/ME, Psychol. Psychother. 90 (2017) 502–509, https://doi.org/10.1111/papt.12118.
[24] V.C. Lombardi, F.W. Ruscetti, J.D. Gupta, M.A. Pfost, K.S. Hagen, D.L. Peterson, S.K. Ruscetti, R.K. Bagni, C. Petrow-Sadowski, B. Gold, Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome, Science 326 (2009) 585–589.
[25] R.K. Naviaux, J.C. Naviaux, K. Li, A.T. Bright, W.A. Alaynick, L. Wang, A. Baxter, N. Nathan, W. Anderson, E. Gordon, Metabolic features of chronic fatigue syndrome, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) E5472–E5480, https://doi.org/10.1073/pnas.1607571113.
[26] M. Loebel, M. Eckey, F. Sotzny, E. Hahn, S. Bauer, P. Grabowski, J. Zerweck, P. Holenya, L.G. Hanitsch, K. Wittke, Serological profiling of the EBV immune response in Chronic Fatigue Syndrome using a peptide microarray, PLoS One 12 (2017) e0179124, , https://doi.org/10.1371/journal.pone.0179124.
[27] W. Eriksen, The spread of EBV to ectopic lymphoid aggregates may be the final common pathway in the pathogenesis of ME/CFS, Med. Hypotheses 102 (2017) 8–15.
[28] M. Loebel, K. Strohschein, C. Giannini, U. Koelsch, S. Bauer, C. Doebis, S. Thomas, N. Unterwalder, V. von Baehr, P. Reinke, Deficient EBV-specific B-and T-cell response in patients with chronic fatigue syndrome, PLoS One 9 (2014) e85387, , https://doi.org/10.1371/journal.pone.0085387.
[29] O.D. Ortega-Hernandez, M. Cuccia, S. Bozzini, N. Bassi, S. Moscavitch, L.M. Diaz-Gallo, M. Blank, N. Agmon-Levin, Y. Shoenfeld, Autoantibodies, polymorphisms in the serotonin pathway, and human leukocyte antigen class II alleles in chronic fatigue syndrome, Ann. N. Y. Acad. Sci. 1173 (2009) 589–599.
[30] N. Agmon-Levin, Y. Zafrir, S. Kivity, A. Balofsky, H. Amital, Y. Shoenfeld, Chronic fatigue syndrome and fibromyalgia following immunization with the hepatitis B vaccine: another angle of the 'autoimmune (auto-inflammatory) syndrome induced by adjuvants'(ASIA), Immunol. Res. 60 (2014) 376–383.
[31] L. Giloteaux, J.K. Goodrich, W.A. Walters, S.M. Levine, R.E. Ley, M.R. Hanson, Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome, Microbiome 4 (2016) 30.
[32] A. Wallis, M. Ball, S. McKechnie, H. Butt, D.P. Lewis, D. Bruck, Examining clinical similarities between myalgic encephalomyelitis/chronic fatigue syndrome and d-lactic acidosis: a systematic review, J. Transl. Med. 15 (2017) 129.
[33] K. Takahashi, H. Terashima, K. Kohno, N. Ohkohchi, A stand-alone synbiotic treatment for the prevention of D-lactic acidosis in short bowel syndrome, Int. Surg. 98 (2013) 110–113.
[34] P. Roman, F. Carrillo-Trabalón, N. Sánchez-Labraca, F. Cañadas, A. Estévez, D. Cardona, Are probiotic treatments useful on fibromyalgia syndrome or chronic fatigue syndrome patients? A systematic review, Benef. Microbes 9 (2018) 603–611, https://doi.org/10.3920/BM2017.0125.
[35] S. Lunde, E.K. Kristoffersen, D. Sapkota, K. Risa, O. Dahl, O. Bruland, O. Mella, Ø. Fluge, Serum BAFF and APRIL levels, T-lymphocyte subsets, and immunoglobulins after B-cell depletion using the monoclonal anti-CD20 antibody rituximab in myalgic encephalopathy/chronic fatigue syndrome, PLoS One 11 (2016) e0161226, , https://doi.org/10.1371/journal.pone.0161226.
[36] Ø. Fluge, O. Mella, Clinical impact of B-cell depletion with the anti-CD20 antibody rituximab in chronic fatigue syndrome: a preliminary case series, BMC Neurol. 9 (2009) 28, https://doi.org/10.1186/1471-2377-9-28.
[37] A. Khanna, L. Jopson, D. Howel, A. Bryant, A. Blamire, J.L. Newton, D.E. Jones, Rituximab is ineffective for treatment of fatigue in primary biliary cholangitis: a phase-2 randomised controlled trial, Hepatology (2018), https://doi.org/10.1002/hep.30099.
[38] G. Anderson, M. Berk, M. Maes, Biological phenotypes underpin the physio-somatic symptoms of somatization, depression, and chronic fatigue syndrome, Acta Psychiatr. Scand. 129 (2014) 83–97.
[39] S.M. Collin, S. Nikolaus, J. Heron, H. Knoop, P.D. White, E. Crawley, Chronic fatigue syndrome (CFS) symptom-based phenotypes in two clinical cohorts of adult patients in the UK and the Netherlands, J. Psychosom. Res. 81 (2016) 14–23.
[40] V. Datieva, A. Rosinskaia, O. Levin, The use of melatonin in the treatment of chronic fatigue syndrome and circadian rhythm disorders in Parkinson's disease (in Russian), Zh. Nevrol. Psikhiatr. Im. S.S. Korsakova 113 (2013) 77–81.
[41] E. Roos, D. Mariosa, C. Ingre, C. Lundholm, K. Wirdefeldt, P.M. Roos, F. Fang, Depression in amyotrophic lateral sclerosis, Neurology 86 (2016) 2271–2277.
[42] M.B. Rietberg, E.E. van Wegen, I.C. Eyssen, G. Kwakkel, MS study group, Effects of multidisciplinary rehabilitation on chronic fatigue in multiple sclerosis: a randomized controlled trial, PLoS One 9 (2014) e107710, , https://doi.org/10.1371/journal.pone.0107710.
[43] E. Agliari, A. Barra, K.G. Vidal, F. Guerra, Can persistent Epstein–Barr virus infection induce chronic fatigue syndrome as a Pavlov reflex of the immune response? J. Biol. Dyn. 6 (2012) 740–762.
[44] A.M. Lerner, M.E. Ariza, M. Williams, L. Jason, S. Beqaj, J.T. Fitzgerald, S. Lemeshow, R. Glaser, Antibody to Epstein-Barr virus deoxyuridine triphosphate nucleotidohydrolase and deoxyribonucleotide polymerase in a chronic fatigue syndrome subset, PLoS One 7 (2012) e47891, , https://doi.org/10.1371/journal.pone.0047891.
[45] J.K. Chia, A.Y. Chia, Chronic fatigue syndrome is associated with chronic enterovirus infection of the stomach, J. Clin. Pathol. 61 (2008) 43–48.
[46] J.G. Montoya, A.M. Kogelnik, M. Bhangoo, M.R. Lunn, L. Flamand, L.E. Merrihew, T. Watt, J.T. Kubo, J. Paik, M. Desai, Randomized clinical trial to evaluate the efficacy and safety of valganciclovir in a subset of patients with chronic fatigue syndrome, J. Med. Virol. 85 (2013) 2101–2109.
[47] M. Meeus, J. Nijs, N. McGregor, R. Meeusen, G. De Schutter, S. Truijen, M. Fremont, E. Van Hoof, K. De Meirleir, Unravelling intracellular immune dysfunctions in chronic fatigue syndrome: interactions between protein kinase R activity, RNase L cleavage and elastase activity, and their clinical relevance, In Vivo 22 (2008) 115–121.
[48] S.E. Shetzline, C. Martinand-Mari, N.L. Reichenbach, Z. Buletic, B. Lebleu, W. Pfleiderer, R. Charubala, K. De Meirleir, P. De Becker, D.L. Peterson, Structural and functional features of the 37-kDa 2-5A-dependent RNase L in chronic fatigue syndrome, J. Interferon Cytokine Res. 22 (2002) 443–456.
[49] M. Frémont, K. El Bakkouri, F. Vaeyens, C.V. Herst, K. De Meirleir, P. Englebienne, 2′, 5′-Oligoadenylate size is critical to protect RNase L against proteolytic cleavage in chronic fatigue syndrome, Exp. Mol. Pathol. 78 (2005) 239–246.
[50] A. Vojdani, P. Choppa, C. Lapp, Downregulation of RNase L inhibitor correlates with upregulation of interferon-induced proteins (2-5A synthetase and RNase L) in patients with chronic fatigue immune dysfunction syndrome, J. Clin. Lab. Immunol. 50 (1998) 1–16.
[51] J. Nijs, K. De Meirleir, Impairments of the 2-5A synthetase/RNase L pathway in chronic fatigue syndrome, In Vivo 19 (2005) 1013–1021.
[52] E.W. Brenu, T.K. Huth, S.L. Hardcastle, K. Fuller, M. Kaur, S. Johnston, S.B. Ramos, D.R. Staines, S.M. Marshall-Gradisnik, Role of adaptive and innate immune cells in chronic fatigue syndrome/myalgic encephalomyelitis, Int. Immunol. 26 (2013) 233–242.
[53] A. Chacko, D.R. Staines, S.C. Johnston, S.M. Marshall-Gradisnik, Dysregulation of protein kinase gene expression in NK cells from chronic fatigue syndrome/myalgic encephalomyelitis patients, Gene Regul. Syst. Bio. 10 (2016) S40036GRSB.
[54] M.V. Lourenco, J.R. Clarke, R.L. Frozza, T.R. Bomfim, L. Forny-Germano, A.F. Batista, L.B. Sathler, J. Brito-Moreira, O.B. Amaral, C.A. Silva, TNF-α mediates PKR-dependent memory impairment and brain IRS-1 inhibition induced by Alzheimer's β-amyloid oligomers in mice and monkeys, Cell Metab. 18 (2013) 831–843.
[55] H. Cabanas, K. Muraki, N. Eaton, C. Balinas, D. Staines, S. Marshall-Gradisnik, Loss of transient receptor potential melastatin 3 ion channel function in natural killer cells from chronic fatigue syndrome/myalgic encephalomyelitis patients, Mol. Med. 24 (2018) 44.
[56] K. Launer-Felty, J.L. Cole, Domain interactions in adenovirus VAI RNA mediate high-affinity PKR binding, J. Mol. Biol. 426 (2014) 1285–1295.
[57] M. Dey, B.R. Mann, A. Anshu, M.A.-u. Mannan, Activation of protein kinase PKR requires dimerization-induced cis-phosphorylation within the activation loop, J. Biol. Chem. 289 (2014) 5747–5757.
[58] M. Maes, F.N. Twisk, K. Ringel, Inflammatory and cell-mediated immune biomarkers in myalgic encephalomyelitis/chronic fatigue syndrome and depression: inflammatory markers are higher in myalgic encephalomyelitis/chronic fatigue syndrome than in depression, Psychother. Psychosom. 81 (2012) 286–295.
[59] M. Maes, F.N. Twisk, M. Kubera, K. Ringel, Evidence for inflammation and activation of cell-mediated immunity in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): increased interleukin-1, tumor necrosis factor-α, PMN-elastase, lysozyme and neopterin, J. Affect. Disord. 136 (2012) 933–939.
[60] J.A. Marcusson, G. Lindh, B. Evengård, Chronic fatigue syndrome and nickel allergy, Contact Derm. 42 (2000) 56–57.
[61] I. Sterzl, J. Procházková, P. Hrdá, J. Bártová, P. Matucha, V.D. Stejskal, Mercury and nickel allergy: risk factors in fatigue and autoimmunity, Neuro Endocrinol. Lett. 20 (1999) 221–228.

[62] K. Lucas, M. Maes, Molecular mechanisms underpinning laser printer and photocopier induced symptoms, including chronic fatigue syndrome and respiratory tract hyperresponsiveness: pharmacological treatment with cinnamon and hydrogen, Neuro Endocrinol. Lett. 34 (2013) 723–737.
[63] V.D. Stejskal, A. Danersund, A. Lindvall, R. Hudecek, V. Nordman, A. Yaqob, W. Mayer, W. Bieger, U. Lindh, Metal-specific lymphocytes: biomarkers of sensitivity in man, Neuro Endocrinol. Lett. 20 (1999) 289–298.
[64] A. Yaqob, A. Danersund, V.D. Stejskal, A. Lindvall, R. Hudecek, U. Lindh, Metal-specific lymphocyte reactivity is down-regulated after dental metal replacement, Neuro Endocrinol. Lett. 27 (2006) 189–197.
[65] S.R. Shin, A.L. Han, Improved chronic fatigue symptoms after removal of mercury in patient with increased mercury concentration in hair toxic mineral assay: a case, Korean J. Fam. Med. 33 (2012) 320–325.
[66] S. Blundell, K. Ray, M. Buckland, P. White, Chronic fatigue syndrome and circulating cytokines: a systematic review, Brain Behav. Immun. 50 (2015) 186–195.
[67] S.N. Pantry, M.M. Medveczky, J.H. Arbuckle, J. Luka, J.G. Montoya, J. Hu, R. Renne, D. Peterson, J.C. Pritchett, D.V. Ablashi, Persistent human herpesvirus-6 infection in patients with an inherited form of the virus, J. Med. Virol. 85 (2013) 1940–1946.
[68] R. Patarca-Montero, T. Mark, M.A. Fletcher, N.G. Klimas, Immunology of chronic fatigue syndrome, J. Chronic Fatigue Syndr. 6 (2000) 69–107.
[69] M.E. Roerink, H. Knoop, E.M. Bronkhorst, H.A. Mouthaan, L.J. Hawinkels, L.A. Joosten, J.W. Meer, Cytokine signatures in chronic fatigue syndrome patients: a Case Control Study and the effect of anakinra treatment, J. Transl. Med. 15 (2017) 267, https://doi.org/10.1186/s12967-017-1371-9.
[70] L. Chen, S.-E. Yoo, R. Na, Y. Liu, Q. Ran, Cognitive impairment and increased Aβ levels induced by paraquat exposure are attenuated by enhanced removal of mitochondrial H_2O_2, Neurobiol. Aging 33 (2012), https://doi.org/10.1016/j.neurobiolaging.2011.01.008 432.e15-26.
[71] R. Wang, V.J. Paul, H. Luesch, Seaweed extracts and unsaturated fatty acid constituents from the green alga Ulva lactuca as activators of the cytoprotective Nrf2–ARE pathway, Free Radic. Biol. Med. 57 (2013) 141–153.
[72] S. Brkic, S. Tomic, D. Maric, A.N. Mikic, V. Turkulov, Lipid peroxidation is elevated in female patients with chronic fatigue syndrome, Med. Sci. Monit. 16 (2010) CR628–CR632.
[73] A.S. Reddi, J.S. Bollineni, Selenium-deficient diet induces renal oxidative stress and injury via TGF-β1 in normal and diabetic rats, Kidney Int. 59 (2001) 1342–1353.
[74] S. Roy, S.K. Dontamalla, A.K. Mondru, S. Sannigrahi, P.R. Veerareddy, Downregulation of apoptosis and modulation of TGF-β1 by sodium selenate prevents streptozotocin-induced diabetic rat renal impairment, Biol. Trace Elem. Res. 139 (2011) 55–71.
[75] Y. Lu, L.M. Wahl, Oxidative stress augments the production of matrix metalloproteinase-1, cyclooxygenase-2, and prostaglandin E2 through enhancement of NF-κB activity in lipopolysaccharide-activated human primary monocytes, J. Immunol. 175 (2005) 5423–5429.
[76] A.P. Simopoulos, Omega-6/omega-3 essential fatty acid ratio and chronic diseases, Food Rev. Int. 20 (2004) 77–90.
[77] S. Edin, M.L. Wikberg, A.M. Dahlin, J. Rutegård, Å. Öberg, P.A. Oldenborg, R. Palmqvist, The distribution of macrophages with a M1 or M2 phenotype in relation to prognosis and the molecular characteristics of colorectal cancer, PLoS One 7 (2012) e47045, , https://doi.org/10.1371/journal.pone.0047045.
[78] M. Nakanishi, A. Menoret, T. Tanaka, S. Miyamoto, D.C. Montrose, A.T. Vella, D.W. Rosenberg, Selective PGE2 suppression inhibits colon carcinogenesis and modifies local mucosal immunity, Cancer Prev. Res. Phila. (Phila) 4 (2011) 1198–1208, https://doi.org/10.1158/1940-6207.CAPR-11-0188.
[79] N. Obermajer, P. Kalinski, Key role of the positive feedback between PGE2 and COX2 in the biology of myeloid-derived suppressor cells, Oncoimmunology 1 (2012) 762–764.
[80] T.L. Whiteside, E.K. Jackson, Adenosine and prostaglandin e2 production by human inducible regulatory T cells in health and disease, Front. Immunol. 4 (2013) 212, https://doi.org/10.3389/fimmu.2013.00212.
[81] E.I. Glover, S.M. Phillips, Resistance exercise and appropriate nutrition to counteract muscle wasting and promote muscle hypertrophy, Curr. Opin. Clin. Nutr. Metab. Care 13 (2010) 630–634.
[82] D. Morris, C. Guerra, C. Donohue, H. Oh, M. Khurasany, V. Venketaraman, Unveiling the mechanisms for decreased glutathione in individuals with HIV infection, Clin. Dev. Immunol. 2012 (2012) 734125, , https://doi.org/10.1155/2012/734125.
[83] N.S. Scrimshaw, Historical concepts of interactions, synergism and antagonism between nutrition and infection, J. Nutr. 133 (2003) 316S–321S.
[84] A.H. Mandarano, L. Giloteaux, B.A. Keller, S.M. Levine, M.R. Hanson, Eukaryotes in the gut microbiota in myalgic encephalomyelitis/chronic fatigue syndrome, Peer J 6 (2018) e4282, https://doi.org/10.7717/peerj.4282.
[85] J. Nijs, G. Nicolson, P. De Becker, D. Coomans, K. De Meirleir, Prevalence of Mycoplasmal infections in European CFS patients. Examination of four Mycoplasma species, FEMS Immunol. Med. Microbiol. 34 (2002) 209–214.
[86] G.L. Nicolson, R. Gan, J. Haier, Evidence for Brucella spp. and Mycoplasma spp. co-infections in blood of Chronic Fatigue Syndrome patients, J. Chronic Fatigue Syndr. 12 (2004) 5–17.
[87] J. Haier, M. Nasralla, A.R. Franco, G.L. Nicolson, Detection of mycoplasmal infections in blood of patients with rheumatoid arthritis, Rheumatol. (Oxford) 38 (1999) 504–509.
[88] G.L. Nicolson, M. Nasralla, K. De Meirleir, Bacterial and viral co-infections in chronic fatigue syndrome (CFS/ME) patients, Proc. Clinical and Scientific Conference on Myalgic Encephalopathy/Chronic Fatigue Syndrome (2002) (Accessed 25 September 2018), https://tinyurl.com/y79auyzw.
[89] M.J. Castaño, J. Solera, Chronic brucellosis and persistence of Brucella melitensis DNA, J. Clin. Microbiol. 47 (2009) 2084–2089.
[90] A. Burri, S. Ogata, G. Livshits, F. Williams, The association between chronic widespread musculoskeletal pain, depression and fatigue is genetically mediated, PLoS One 10 (2015) e0140289, , https://doi.org/10.1371/journal.pone.0140289.
[91] A.C. Logan, C. Wong, Chronic fatigue syndrome: oxidative stress and dietary modifications, Altern. Med. Rev. 6 (2001) 450–460.
[92] G. Nicolson, R. Gan, J. Haier, Multiple co-infections (mycoplasma, chlamydia, human herpes virus-6) in blood of chronic fatigue syndrome patients: association with signs and symptoms, APMIS 111 (2003) 557–566.
[93] R. Richards, T. Roberts, N. McGregor, R. Dunstan, H. Butt, Blood parameters indicative of oxidative stress are associated with symptom expression in chronic fatigue syndrome, Redox Rep. 5 (2000) 35–41.
[94] N.R. Wawrzyniak, A.M. Joseph, D.G. Levin, D.M. Gundermann, C. Leeuwenburgh, B. Sandesara, T.M. Manini, P.J. Adhihetty, Idiopathic chronic fatigue in older adults is linked to impaired mitochondrial content and biogenesis signaling in skeletal muscle, Oncotarget 7 (2016) 52695–52709, https://doi.org/10.18632/oncotarget.10685.
[95] C.W. Armstrong, N.R. McGregor, D.P. Lewis, H.L. Butt, P.R. Gooley, Metabolic profiling reveals anomalous energy metabolism and oxidative stress pathways in chronic fatigue syndrome patients, Metabolomics 11 (2015) 1626–1639.
[96] Y. Jammes, J. Steinberg, O. Mambrini, F. Bregeon, S. Delliaux, Chronic fatigue syndrome: assessment of increased oxidative stress and altered muscle excitability in response to incremental exercise, J. Intern. Med. 257 (2005) 299–310.
[97] M. Maes, I. Mihaylova, J.-C. Leunis, Chronic fatigue syndrome is accompanied by an IgM-related immune response directed against neopitopes formed by oxidative or nitrosative damage to lipids and proteins, Neuro Endocrinol. Lett. 27 (2006) 615–622.
[98] S. Fukuda, J. Nojima, Y. Motoki, K. Yamaguti, Y. Nakatomi, N. Okawa, K. Fujiwara, Y. Watanabe, H. Kuratsune, A potential biomarker for fatigue: oxidative stress and anti-oxidative activity, Biol. Psychol. 118 (2016) 88–93.
[99] G. Kennedy, V.A. Spence, M. McLaren, A. Hill, C. Underwood, J.J. Belch, Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms, Free Radic. Biol. Med. 39 (2005) 584–589.
[100] G. Morris, M. Maes, A neuro-immune model of myalgic encephalomyelitis/chronic fatigue syndrome, Metab. Brain Dis. 28 (2013) 523–540.
[101] T. Nguyen, D. Staines, B. Nilius, P. Smith, S. Marshall-Gradisnik, Novel identification and characterisation of Transient receptor potential melastatin 3 ion channels on Natural Killer cells and B lymphocytes: effects on cell signalling in Chronic fatigue syndrome/Myalgic encephalomyelitis patients, Biol. Res. 49 (2016) 27, https://doi.org/10.1186/s40659-016-0087-2.
[102] A. Bradley, B. Ford, A. Bansal, Altered functional B cell subset populations in patients with chronic fatigue syndrome compared to healthy controls, Clin. Exp. Immunol. 172 (2013) 73–80.
[103] M. Maes, E. Bosmans, M. Kubera, Increased expression of activation antigens on CD8+ T lymphocytes in Myalgic Encephalomyelitis/chronic fatigue syndrome: inverse associations with lowered CD19+ expression and CD4+/CD8+ ratio, but no associations with (auto) immune, leaky gut, oxidative and nitrosative stress biomarkers, Neuro Endocrinol. Lett. 36 (2015) 439–446.
[104] E. Fenouillet, A. Vigouroux, J.G. Steinberg, A. Chagvardieff, F. Retornaz, R. Guieu, Y. Jammes, Association of biomarkers with health-related quality of life and history of stressors in myalgic encephalomyelitis/chronic fatigue syndrome patients, J. Transl. Med. 14 (2016) 251.
[105] R.D. Petty, N.E. McCarthy, R. Le Dieu, J.R. Kerr, MicroRNAs hsa-miR-99b, hsa-miR-330, hsa-miR-126 and hsa-miR-30c: potential diagnostic biomarkers in natural killer (NK) cells of patients with chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME), PLoS One 11 (2016) e0150904, , https://doi.org/10.1371/journal.pone.0150904.
[106] B.A. Lidbury, B. Kita, D.P. Lewis, S. Hayward, H. Ludlow, M.P. Hedger, D.M. Kretser, Activin B is a novel biomarker for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) diagnosis: a cross sectional study, J. Transl. Med. 15 (2017) 60, https://doi.org/10.1186/s12967-017-1161-4.
[107] M.R. Werbach, Nutritional strategies for treating chronic fatigue syndrome, Altern. Med. Rev. 5 (2000) 93–108.
[108] B. Regland, S. Forsmark, L. Halaouate, M. Matousek, B. Peilot, O. Zachrisson, C.G. Gottfries, Response to vitamin B12 and folic acid in myalgic encephalomyelitis and fibromyalgia, PLoS One 10 (2015) e0124648, , https://doi.org/10.1371/journal.pone.0124648.
[109] K. Miwa, M. Fujita, Fluctuation of serum vitamin E (α-tocopherol) concentrations during exacerbation and remission phases in patients with chronic fatigue syndrome, Heart Vessels 25 (2010) 319–323.
[110] D. Maric, S. Brkic, A.N. Mikic, S. Tomic, T. Cebovic, V. Turkulov, Multivitamin mineral supplementation in patients with chronic fatigue syndrome, Med. Sci. Monit. 20 (2014) 47–53, https://doi.org/10.12659/MSM.889333.
[111] G.L. Nicolson, R. Ellithorpe, Lipid replacement and antioxidant nutritional therapy for restoring mitochondrial function and reducing fatigue in chronic fatigue syndrome and other fatiguing illnesses, J. Chronic Fatigue Syndr. 13 (2006) 57–68.
[112] M. Houston, Lipid Replacement Therapy with a glycophospholipid-antioxidant-vitamin formulation significantly reduces fatigue within one week, J. Am. Nutraceut. Assoc. 13 (2010) 10–14.
[113] N.S. Porter, L.A. Jason, A. Boulton, N. Bothne, B. Coleman, Alternative medical interventions used in the treatment and management of myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia, J. Altern. Complement. Med. 16 (2010) 235–249, https://doi.org/10.1089/acm.2008.0376.
[114] N. Campagnolo, S. Johnston, A. Collatz, D. Staines, S. Marshall-Gradisnik, Dietary

and nutrition interventions for the therapeutic treatment of chronic fatigue syndrome/myalgic encephalomyelitis: a systematic review, J. Hum. Nutr. Diet. 30 (2017) 247–259.

[115] M.L. Joustra, I. Minovic, K.A. Janssens, S.J. Bakker, J.G. Rosmalen, Vitamin and mineral status in chronic fatigue syndrome and fibromyalgia syndrome: a systematic review and meta-analysis, PLoS One 12 (2017) e0176631, , https://doi.org/10.1371/journal.pone.0176631.

[116] K. Jones, Y. Probst, Role of dietary modification in alleviating chronic fatigue syndrome symptoms: a systematic review, Aust. N. Z. J. Public Health 41 (2017) 338–344.

[117] J.E. Teitelbaum, C. Johnson, J. St Cyr, The use of D-ribose in chronic fatigue syndrome and fibromyalgia: a pilot study, J. Altern. Complement. Med. 12 (2006) 857–862.