Chronic Fatigue Syndrome: Oxidative Stress and Dietary Modifications

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Abstract

Chronic fatigue syndrome (CFS) is an illness characterized by persistent and relapsing fatigue, often accompanied by numerous symptoms involving various body systems. The etiology of CFS remains unclear; however, a number of recent studies have shown oxidative stress may be involved in its pathogenesis. The role of oxidative stress in CFS is an important area for current and future research as it suggests the use of antioxidants in the management of CFS. Specifically, the dietary supplements glutathione, N-acetylcysteine, alpha-lipoic acid, oligomeric proanthocyanidins, *Ginkgo biloba*, and *Vaccinium myrtillus* (bilberry) may be beneficial. In addition, research on food intolerance is discussed, since food intolerance may be involved in CFS symptom presentation and in oxidation via cytokine induction. Finally, recent evidence suggests celiac disease can present with neurological symptoms in the absence of gastrointestinal symptoms; therefore, celiac disease should be included in the differential diagnosis of CFS.

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Introduction

Chronic fatigue syndrome (CFS) is a relatively common disorder, particularly in women, affecting 522 women and 291 men per 100,000.[1] In addition to the characteristic persistent fatigue, CFS patients often complain of a number of symptoms including headache, joint pain, gastrointestinal (GI) disturbance, cognitive dysfunction, visual disturbance, and paresthesia.[2, 3]

Pathological changes have been observed in CFS patients, including white matter lesions in the CNS[4-6] and cerebral hypoperfusion.[7-9] Other findings that suggest CNS involvement include vestibular dysfunction[10,11] and gait abnormalities.[12,13] Immune response also appears to be impaired; specifically, elevated levels of interferon alpha, transforming growth factor beta, interleukin-4, interleukin-6, interleukin-1 alpha, and tumor necrosis factor alpha (TNF-α) have been observed.[14-19]

The purpose of this paper is to integrate various branches of current research in an effort to highlight the importance of antioxidant capacity and food intolerance in CFS. First, recent studies will be reviewed that indicate oxidative stress is involved in the pathogenesis of CFS. This suggests antioxidants may be beneficial in the management of CFS. Glutathione (GSH), N-acetylcysteine (NAC), α-lipoic acid, oligomeric proanthocyanidins (OPCs), *Ginkgo biloba*,

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and *Vaccinium myrtillus* (bilberry) would therefore be dietary supplements with potential therapeutic benefit. Second, the literature will be reviewed that suggests food intolerance may be involved in CFS symptom presentation and in oxidation via cytokine induction.

Although food intolerance can be an important consideration in the presentation of this heterogeneous disorder, evidence also suggests celiac disease should be included in the differential diagnosis of CFS. Celiac disease may present primarily with neurological symptoms in the absence of gastrointestinal symptoms.

Current Research on Oxidative Stress in CFS

The role of oxidative stress in CFS is an emerging focus of research. Although it is uncertain whether oxidative stress is a cause or a result of this illness, recent studies have demonstrated that oxidative stress contributes to the pathology and clinical symptoms of CFS. Theoretically, oxidative stress can be caused by an increase in the generation of reactive oxygen species, of which mitochondrial dysfunction is believed to be a main source, or it can be caused by a decline in the efficiency of antioxidant enzyme systems.[20] Recent studies have examined both of these possibilities by looking for markers of oxidative stress and protective antioxidant systems.

Fulle et al observed evidence of oxidative damage to the DNA and lipids of biopsy samples from the vastus lateralis muscles of CFS patients.[20] In addition, they found an increase in the activity of antioxidant enzyme systems, including glutathione peroxidase, an increase they suggest is a compensatory measure in response to oxidative stress. The researchers noted a similarity between increased oxidative damage in CFS patients and age-related changes in healthy individuals, concluding that antioxidants have therapeutic potential to reduce oxidative damage.

Pall suggests the level of the oxidant peroxynitrite is important in CFS patients.[21] He contends elevated peroxynitrite causes mitochondrial dysfunction, lipid peroxidation, and, by way of positive feedback, elevated cytokine levels. The cytokines, in turn, cause the formation of nitric oxide that combines with superoxide to form the potent oxidant peroxynitrite, thus continuing the cycle. Peroxynitrite targets the mitochondria and Pall notes this may help explain mitochondrial dysfunction in CFS. As support for the peroxynitrite theory, Pall cites evidence that the mitochondrial enzymes succinic dehydrogenase and cis-aconitase are inactivated by peroxynitrite.[22,23] This makes for an interesting finding because decreased succinic dehydrogenase activity has been found in CFS patients[24,25] and urine levels of the intermediates metabolized by these enzymes have been found to be elevated in CFS patients.[26,27] Pall proposes a number of nutritional and botanical interventions that may reduce peroxynitrite and cytokine levels; among them, the soy isoflavone genistein, epigallocatechin-3-gallate from green tea, and vitamins C and E.

Keenoy et al found impaired antioxidant capacity in a sample of CFS patients with "subclinical" or moderate magnesium deficiency.[28] The impaired capacity involved both the total antioxidative capacity of plasma, as measured by Trolox Equivalents Antioxidant Capacity (TEAC), and the antioxidant component dependent on albumin. While no improvement was observed in these parameters after oral or intravenous magnesium supplementation, some patients demonstrated increased serum vitamin E and an associated decrease in lipid peroxidation. This finding, according to the authors, is likely due to the sparing effect of magnesium on vitamin E by preventing its *in vivo* oxidation. In addition, the researchers postulated that an elevated concentration of inflammatory cytokines might indirectly cause diminished antioxidant capacity by inhibiting albumin transcription in the liver.

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A subset of patients whose magnesium body stores did not improve after supplementation also had lower blood glutathione levels, suggesting a relationship might exist between intractable magnesium deficiency and low glutathione.[28] Interestingly, RBC magnesium levels have previously been reported to be decreased in CFS patients, some of whom had adequate dietary intake of magnesium.[29]

Some of these same researchers further examined the role of oxidative stress in CFS. They found an increased susceptibility of LDL and VLDL to copper-induced peroxidation in CFS patients.[30] They conclude this might indicate the impaired lipoprotein antioxidant capacity in CFS, causing accelerated lipid peroxidation.

Richards et al found CFS patients had elevated levels of methemoglobin (MetHb), a marker of oxidative stress.[31] Formation of MetHb, a product of iron oxidation, is regulated by NADH-MetHb reductase. Consequently, levels of MetHb may increase when there is an alteration in this reducing system within the erythrocyte. The researchers reported the increase in MetHb correlates with the presence and severity of several CFS symptoms, including photophobia, irritability, and GI complaints. MetHb also requires glutathione and cysteine to be reduced in normal cells. It is interesting to note that both glutathione[28] and cysteine[32] levels have been found in decreased levels in CFS patients.

Additional evidence supporting the role of free radical damage in CFS patients and the efficacy of antioxidant treatment comes from a recent study.[33] In a three-month, double-blind, placebo-controlled crossover study, 22 CFS patients were given a Swedish pollen extract high in antioxidant polyphenols. Statistically significant improvement was observed in the treatment group, notably in fatigue, sleep disturbance, GI complaints, and hypersensitivity. In addition, there was a highly significant improvement in erythrocyte fragility, a marker of oxidative damage. The researcher acknowledged the synergistic effect of antioxidants, as in the Swedish pollen extract, and suggests future research using antioxidant combinations.

Implications for Antioxidant Treatment

The above findings on oxidative stress suggest that supplementing with certain antioxidants, in addition to vitamins C and E, may be valuable in a CFS treatment protocol (Table 1). A number of supplements should be considered for potential therapeutic intervention, including selenium (necessary to support glutathione peroxidase activity),[34] GSH, NAC, and α-lipoic acid. Although there is conflicting evidence, a number of studies have shown oral administration of GSH can directly increase plasma and tissue GSH concentration.[35-37] Alternately, NAC and α-lipoic acid can increase GSH concentration indirectly;[38,39] NAC provides cysteine for GSH synthesis, and α-lipoic acid is believed to increase intracellular GSH levels by reducing extracellular cystine to cysteine, bypassing the cystine transporter.[40] GSH is neuroprotective and may play a role in preventing additional CNS lesions.[41] α-Lipoic acid is also neuroprotective, scavenges nitric oxide and peroxynitrite, and may be especially promising as an antioxidant against mitochondrial dysfunction.[40] The supplement coenzyme Q10 has similar neuroprotective qualities and has the ability to improve mitochondrial function.[42]

The botanical antioxidants OPCs and *Ginkgo biloba* should also be considered. Bagchi et al found that OPCs are highly bioavailable and provide significantly greater protection against free radical damage than beta carotene and vitamins C and E.[43] These authors also reported the ability of OPCs to provide protection from radical-induced lipid peroxidation and DNA damage, which is of particular importance to CFS patients.

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Table 1. Antioxidants in the Treatment of CFS and Their Mechanisms

Antioxidant	Mechanism of Action
Selenium	Supports glutathione peroxidase activity, a Se-dependant antioxidant system[34]
Glutathione	Reduced glutathione (GSH) directly increases glutathione levels[35-37]
N-acetylcysteine	Provides cysteine for GSH synthesis[38]
α-Lipoic acid	Increases intracellular GSH by reducing extracellular cystine to cysteine[40]
CoQ10	Improves mitochondrial function; neuroprotective[42]
Oligomeric proanthocyanidins	Protects against radical-induced lipid peroxidation and DNA damage[43]
Ginkgo biloba	Powerful antioxidant; increases cerebral perfusion and associated memory and cognitive deficits; neuroprotective[45-47]
Vaccinium myrtillus (bilberry)	Neuroprotective;[52] protects RBCs from in vivo oxidative damage[53]

Ginkgo biloba is a powerful antioxidant,[44] demonstrating strong neuroprotective properties in animals. It has been shown to reduce mitochondrial reactive oxygen species, in particular peroxynitrite.[45] The capacity of Ginkgo to increase cerebral blood flow[46] and improve memory and cognition associated with cerebral insufficiency[47] suggests it may be useful for CFS symptoms related to hypoperfusion.

Plant-based antioxidant support should be maximized through dietary intake. Cao et al found that a diet high in fruits and vegetables can increase plasma antioxidant capacity in humans, as measured by oxygen radical absorbance capacity (ORAC) assay.[48] Blueberries have the highest ORAC scores among thirty fruits and vegetables tested,[49,50] and may be of significant benefit due to their high potential antioxidant activity,[51] neuroprotective properties,[52] and specific ability to protect red blood cells from *in vivo* oxidative damage.[53] Of the blueberry species, *Vaccinium myrtillus* has the highest combined anthocyanidin, phenol, and ORAC scores.[51]

In a recent double-blind, placebo-controlled, crossover study, administration of pure anthocyanidins (80 mg daily) showed a small but statistically significant benefit in a group of patients with the related disorder of fibromyalgia.[54] The trial was three months in duration for active treatment and involved an anthocyanidin combination derived from grape seed, bilberry, and cranberry. Improvements were observed in sleep quality and fatigue. Based on these findings a similar trial is warranted in CFS patients.

Food Intolerance, Cytokines, and CFS

Food intolerance is implicated in the presentation of symptoms in CFS. Nisenbaum et al presented an abstract at the American Association for Chronic Fatigue Syndrome conference in Seattle in January 2001, show-

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ing that 54 percent of a sample of CFS patients had attempted unspecified dietary modifications. Of these individuals who modified their diet, 73 percent reported dietary changes were beneficial in reducing fatigue.[55] It remains speculative whether these improvements were due to increased dietary antioxidant intake or the elimination of certain foods. Although further research is necessary, it appears diet plays an important role in CFS, in contrast to previous suggestions.[29]

Recent research published in *Lancet* by Jacobsen et al suggests that eliminating food intolerances by dietary modification may reduce the release of inflammatory cytokines.[56] The investigators demonstrated that individuals with food intolerance, a condition distinguished from IgE-mediated food allergy, had a significant elevation in inflammatory cytokines (interleukin-4, interferon gamma, TNF-α) when given a dietary challenge of dairy and wheat. The authors noted that cytokine elevations can account for post-challenge symptoms such as headache, myalgia, joint pain, and GI disturbance, symptoms clearly similar to those observed in CFS patients.

Prior to the *Lancet* study, researchers had made assumptions regarding food intolerance and chronic fatigue. Manu et al, without conducting an elimination and challenge diet or evaluating for the presence of inflammatory markers, suggested that patients with chronic fatigue who report food intolerance are merely manifesting somatization traits.[57] Food intolerance was identified by asking patients to name foods causing adverse reactions. This is not a reliable method, since the inflammatory response is neither as immediate nor as extreme as in classic food allergy, making self-identification of offending foods difficult. The landmark study by Jacobsen et al[56] validates the symptoms of those with food intolerance and thereby negates those false assumptions of the presence of psychiatric pathology.

There are a number of diagnostic methods to detect the presence of food intolerance, the "gold standard" being the elimination and challenge diet.[58] Research has shown the use of a food and symptom diary during the elimination and challenge diet further helps to identify problem foods.[59] In addition to being an inexpensive method to determine whether a food or chemical intolerance is contributing to the symptoms of CFS, subsequent elimination of the offending foods or additives from the diet may be an effective treatment. This protocol has been successful for other illnesses, including asthma,[60] ulcerative colitis,[61] Crohn's disease,[62] irritable bowel syndrome (IBS),[63] and perennial rhinitis.[64]

In an Australian study, CFS patients eliminated wheat, milk, benzoates, nitrites, nitrates, and food colorings and other additives from their diet.[65] The compliance rate was approximately 50 percent, with 37 patients completing the protocol. Of the CFS patients who complied, the results were remarkable: 90 percent reported improvement in the severity of symptoms across multiple body symptoms, with significant reduction in fatigue, recurrent fever, sore throat, muscle pain, headache, joint pain, and cognitive dysfunction. Furthermore, the elimination protocol resulted in a marked improvement in IBS-like symptoms among all patients; a significant finding because CFS patients have a high rate of IBS.[66,67]

The results of this study support the findings of Borok published in the *South African Medical Journal* over a decade ago.[68] Borok cited a strong correlation between CFS and the presence of food intolerance. He reported alleviation of chronic fatigue among CFS patients (n=20) after removing certain foods from the diet, with milk, wheat, and corn among the top offenders.

Gibson and Gibson explored the effect of intolerance to wheat on CFS symptoms in a pilot study.[69] They used a multi-therapeutic protocol that included a wheat-free diet, nutritional supplementation, and homeopathy.

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After four months, 70 percent of the 64 patients enrolled in the study showed improvement in physical symptoms and mental outlook. Unfortunately, due to the study design, it is impossible to know what effect elimination of wheat alone might have had.

Another study concluded that choosing organically grown dietary fruits and vegetables is important for CFS patients, since they have elevated serum levels of chlorinated hydrocarbon pesticides compared to normal control subjects.[70] The authors noted that certain chlorinated hydrocarbon pesticides, such as 1,1-dichloro-2,2-bis(P-chlorophenyl)ethene (DDE), are lipid compounds that can accumulate in cell membranes and may alter cell membrane integrity and inhibit functional membrane-bound proteins. Moreover, they are capable of crossing the blood-brain barrier to affect neurological activity. With respect to food intolerance, exposure to pesticides may be involved in the loss of innate or natural tolerance for chemicals, including those in foods.[71]

Interestingly, Komaroff et al found 60 percent of CFS patients reported alcohol intolerance at the onset of CFS.[3] This is similar to the experience of those having the related illnesses of multiple chemical sensitivity (MCS) and Gulf War syndrome (GWS). Miller and Prihoda found MCS and GWS patients frequently report alcohol and food intolerance.[71] They discussed the possibility that alcohol intolerance may be related to food sensitivity to the grain or fruit from which the alcohol is derived.

Celiac Disease May Mimic CFS

Keeping in mind that CFS is a disorder of exclusion and that there have been reports of improvements with wheat elimination, all patients should be assessed for the presence of celiac disease (CD). Investigators have found CD to be an under-diagnosed condition in the general population[72] and may present with only mild enteropathy or no GI symptoms at all.[73] Neurological dysfunction is a known complication of CD and ataxia, and cognitive difficulties may be the first manifestations of clinically-silent celiac disease.[74]

In an article published in *Lancet*, Hadjivassiliou et al demonstrated that 57 percent of 53 individuals with neurological dysfunction of unknown cause had positive antigliadin antibodies.[75] Most of these patients did not manifest major GI symptoms that would lead a clinician to consider CD.

Luostarinen et al, in a recent review article on celiac disease published in *European Neurology*, stated that CD should be considered in all patients presenting with neurological disturbances such as memory deficits and ataxia of unknown etiology.[76] Assuming that GI complaints, gait abnormalities, cognitive difficulties, and other neurological complaints are common among CFS patients, an investigation into CD is warranted. A preliminary investigation has not established a clinical link between CFS and CD;[77] however, the prevalence of CD may be higher among CFS patients than in the general population.[77,78] The current case definition for CFS[79] has been criticized for not suggesting lab work to determine the presence of celiac disease, resulting in CD being overlooked and presumed to be CFS.[80] Clinicians should be aware that reduced levels of serum ferritin and decreased red cell folate are sensitive laboratory observations (88 percent and 82 percent, respectively) in routine screening of celiac patients.[81]

Conclusion

Despite extensive international research, both the etiology and pathogenesis of CFS are far from clear. A number of recent studies demonstrate that oxidative stress is a component of the illness, although further research is needed to elucidate whether the oxidative damage is the cause or an effect. Since it is apparent from the research presented that some degree of oxidative stress is present in

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CFS patients, various antioxidants show promise as part of a CFS protocol. The antioxidants glutathione, N-acetylcysteine, α-lipoic acid, oligomeric proanthocyanidins, *Ginkgo biloba*, and *Vaccinium myrtillus* very possibly hold promise, although clinical studies are necessary to demonstrate their efficacy among CFS patients.

With respect to diet, information on food intolerance and CFS remains limited. Perhaps new research will determine if food intolerance plays a direct role in cytokine induction among CFS patients. Until this research is conducted and the mechanisms behind this complex illness are more fully understood, elimination and challenge diets combined with the synergistic effects of multiple dietary and supplemental antioxidants may be beneficial in a CFS treatment protocol.

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