

# Chronic Fatigue Syndrome: A Personalized Integrative Medicine Approach

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## ABSTRACT

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a relatively common illness, yet despite considerable investigation, current treatments have modest benefits, and the prognosis remains poor. Because CFS/ME is a heterogeneous disorder with diverse etiological factors and pathological features, a patient-centered integrative framework based on modifiable physiological and environmental factors may offer hope for more effective management and better clinical outcomes. An individualized approach may also help target interventions for subgroups most likely to respond to specific

treatments. This review summarizes a number of avenues for integrative management, including dietary modification, functional nutritional deficiencies, physical fitness, psychological and physical stress, environmental toxicity, gastrointestinal disturbances, immunological aberrations, inflammation, oxidative stress, and mitochondrial dysfunction. A personalized, integrative approach to CFS/ME deserves further consideration as a template for patient management and future research. (*Altern Ther Health Med.* 2014;20(1):29-40.)

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Chronic unexplained fatigue is a very common clinical complaint. In primary care settings, an estimated 24% of patients report fatigue as a significant problem, and population estimates for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) range from 1.85% to 11.3%.<sup>1</sup> Despite the high prevalence of CFS/ME and considerable research on the disease, the amount of time required to diagnose it remains long, and its prognosis continues to be poor. Diagnosis takes an average of 5 years from initiation of symptoms to identification of the syndrome, with total recovery rates between 0% and 37% and rates of improvement between 6% and 63%.<sup>2</sup> The poor prognosis for CFS/ME in part may be due to its heterogeneous nature, and like many chronic diseases, it has a number of etiological and functional disturbances that contribute to the disease's course and symptoms.

Although the exact cause of CFS/ME is unknown, several underlying and sometimes characteristic states of physi-

ological dysfunction have been identified; in particular, abnormalities of the immune and central nervous systems have been found.<sup>3</sup> These findings have led some researchers to suggest that looking for the cause of CFS/ME is a self-defeating exercise; they suggest that focusing on rehabilitation and improvement of functional status is more important.<sup>4</sup> This notion leads to the possibility of creating an integrative management approach that is grounded in the hypothesis that CFS/ME is the manifestation of a complex state of physiological dysfunction unique to an individual.<sup>5</sup>

Integrative medicine involves the application of a patient-centered, individualized approach to disease management that incorporates the best available treatment options, including conventional and evidence-based complementary and alternative medicine.<sup>6</sup> To this end, the practitioner may evaluate physiological function during assessment, while treatments typically may incorporate environmental, lifestyle, mind-body, dietary, and nutraceutical interventions. The aim of this review is to explore modifiable environmental and physiological factors that may play a role in CFS/ME and to discuss the current evidence for corresponding treatments from an integrative perspective.

## CLINICAL ASSESSMENT AND DEFINITION

The current method of diagnosis of CFS/ME is based on exclusion of alternative explanations for fatigue, and no accepted, standard investigative tests exist that can confirm

or refute a diagnosis.<sup>7</sup> The most commonly accepted symptom criterion is the 1994 case definition for CFS/ME from the Centers for Disease Control and Prevention (CDC).<sup>8</sup>

According to this definition, an individual must satisfy 2 criteria to be diagnosed with CFS. The individual (1) must have self-reported, persistent or relapsing fatigue for at least 6 consecutive months, and other medical conditions for which manifestation includes fatigue must be excluded by clinical diagnosis and (2) must have 4 or more of the following symptoms concurrently: postexertional malaise, impaired memory or concentration, unrefreshing sleep, muscle pain, multijoint pain without redness or swelling, tender cervical or axillary lymph nodes, sore throat, or headache—that must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue.

Scientists have also noted that children may differ in presentation from adults with CFS/ME, displaying symptoms such as sadness, hyperactivity (initial phase), episodic tension headaches, abdominal pain, tachycardia, and orthostatic hypotension. Notably CFS/ME in children may be mistaken for laziness or school phobia.<sup>9</sup>

Routine clinical investigations are recommended by the UK National Institute of Clinical Excellence to exclude medical causes of chronic fatigue, and additional serology should be done to exclude bacterial and/or viral involvement if the individual's history suggests the possibility of a recent infection.<sup>10</sup>

Individuals with CFS/ME should also be evaluated for psychiatric illnesses, as symptoms of depression and psychological stress are commonly associated with the condition.<sup>11</sup> Although depressive disorder may be an important diagnostic exclusion, a number of important features can indicate a concomitant presentation of CFS/ME with depression.

Differential symptoms of CFS/ME with depression compared to primary depression include the following: (1) individuals with CFS/ME lack feelings of anhedonia (inability to experience pleasure, guilt, and decreased motivation that is classically seen in individuals with depression); (2) individuals experience several CFS/ME symptoms, including prolonged fatigue after physical exertion, night sweats, sore throats, and swollen lymph nodes, which are not commonly found in depression; (3) fatigue is the principal feature of CFS/ME but does not assume equal prominence in depression; and (4) illness onset with CFS/ME is often sudden, occurring over a few hours or days, whereas primary depression generally shows a more gradual onset.<sup>12,13</sup>

Most important, CFS/ME shares many symptomatic features with other functional somatic syndromes, including irritable bowel syndrome (IBS), fibromyalgia (FM), multiple chemical sensitivity, headaches, and temporomandibular joint dysfunction.<sup>14</sup> Overlap between CFS/ME and FM is particularly common, with approximately 20% to 75% of individuals with CFS/ME meeting the criteria for FM.<sup>15-17</sup>

Currently recommended treatments for CFS/ME include cognitive behavior therapy (CBT) and graded exercise therapy (GET), and no suggested pharmacological

therapies are available.<sup>18</sup> Clinical improvements, however, are modest, with some 40% to 50% of patients reporting improvements in fatigue after treatment with CBT or GET versus 20% to 30% in usual care. Furthermore, the generalizability of findings from randomized, controlled trials to real-world clinical settings is contentious, and long-term treatment outcomes are uncertain.<sup>19</sup>

The effects of GET and CBT on disability and quality of life are discouraging. At 12 months, health-related quality of life was not shown to improve with CBT and GET versus usual care; in fact, physical function and scores for bodily pain were worse in the intervention group.<sup>20</sup> One study examined the impact of interventions, including GET and CBT, on disability, as indicated primarily by the ability to work.<sup>21</sup> It concluded that no currently available intervention was able to restore functional status (ie, the ability to work).

The apparent limitations of current treatments, coupled with the diverse etiopathogenesis of CFS/ME, has led some investigators to suggest that an individually tailored approach to treatment, which takes into account a patient's unique pathological features and employs corresponding evidence-based treatments, may be a more rational approach to patient management.<sup>19</sup>

A number of modifiable physiological and environmental factors have been investigated as contributors to CFS/ME. These factors include dietary and nutritional factors, physical fitness, psychological and physical stress, various environmental pollutants, gastrointestinal disturbances, chronic infection, inflammation and oxidative stress, and mitochondrial dysfunction (Figure 1).

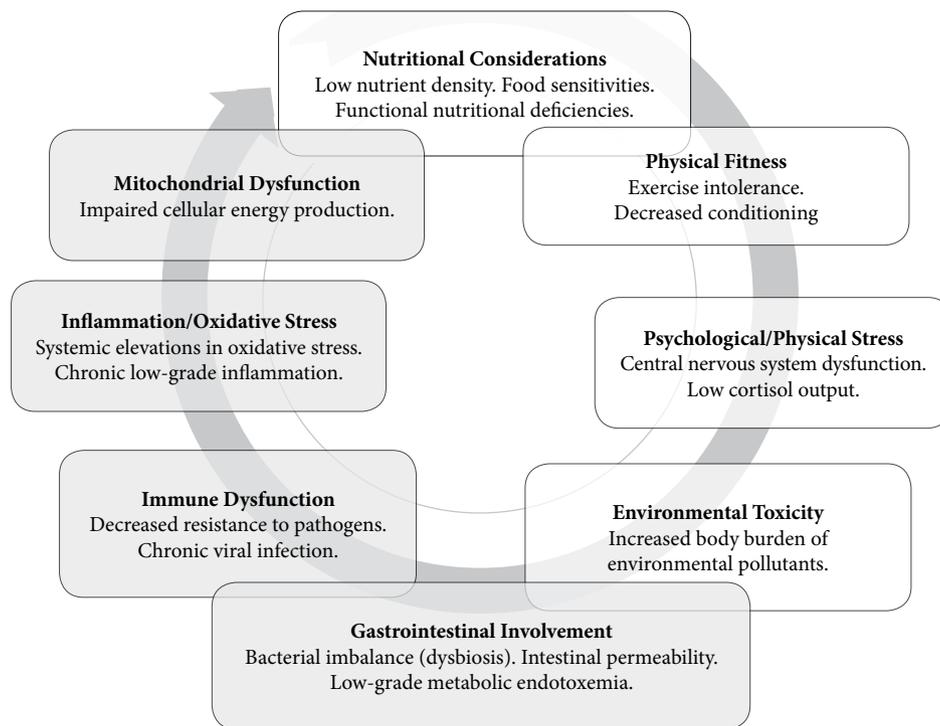
In this review, the author explores each of these categories sequentially, briefly discussing supportive evidence for their contribution to CFS/ME and then investigating potential treatments, including behavioral, mind-body, dietary, lifestyle, and nutraceutical interventions.

## DIETARY AND GENERAL NUTRITIONAL CONSIDERATIONS

Although diet is known to be a potent modifier of several chronic diseases, investigations of diet in CFS/ME are lacking. One investigation found no relationship between current dietary habits—including intake of alcohol, fat, fibers, fruit, and vegetables—and fatigue severity or functional impairments in individuals with CFS/ME.<sup>22</sup> Although individuals with CFS/ME tended to lead healthier lifestyles compared to the general population, in one study, 70% had unhealthy fat, fruit, and vegetable intake, and 95% had unhealthy fiber intake.<sup>22</sup>

It is plausible to suggest that dietary intervention could improve functional status in CFS/ME, considering that a healthy dietary pattern such as a traditional Mediterranean-style diet could counter functional impairments, such as low-grade inflammation and oxidative stress, and improve mental vigor, mood, and physical fitness.<sup>23-27</sup> Some evidence that supports this hypothesis comes from a dietary intervention with high-polyphenol dark chocolate. In this study, eating

**Figure 1.** Modifiable Physiological and Environmental Factors



dark chocolate for 8 weeks—15 grams, 3 times per day—significantly reduced fatigue, increased physical activity, and reduced anxiety and depression in CFS/ME sufferers.<sup>28</sup> Phytonutrient-dense, polyphenol-rich foods are thought to be a major reason for the beneficial effects of a traditional Mediterranean-style diet.<sup>29</sup>

Food sensitivities may play a role in chronic unexplained fatigue. One investigation reportedly found that the elimination of wheat, milk, benzoates, nitrites, nitrates, food additives, and food colorings resulted in a significant improvement in CFS/ME symptoms of fatigue, recurrent fever, sore throat, muscle pain, headache, joint pain, cognitive dysfunction, and IBS.<sup>30</sup> In addition, celiac disease is commonly associated with fatigue, which improves on a gluten-free diet; however the possibility of a relationship between CFS/ME and gluten sensitivity has not been investigated.<sup>31</sup>

**Functional Nutritional Deficiencies**

Functional nutrition is a paradigm grounded in the notion that unique imbalances in nutritional status can give rise to changes in physiological function that may ultimately influence the expression of disease.<sup>32</sup> The functional-nutrition model is a patient-centered approach that is concerned with identifying nutritional imbalances unique to an individual and correcting them through diet and/or nutritional supplementation to restore healthy physiological function. A number of functional nutritional deficiencies have been identified in CFS/ME. While nutrient interventions are likely to have small effect sizes and considerable variations in treatment response in studies, it is important to consider that

they may still offer benefit to the individual, and they have an excellent safety profile.<sup>33</sup>

**Vitamin D.** A retrospective survey of serum levels of 25-hydroxyvitamin D (25[OH]D) in individuals with CFS/ME found that vitamin D levels were significantly lower compared to the general population, with a mean of 44.4 nmol/L (optimal levels > 75 nmol/L).<sup>34</sup> Researchers have hypothesized that vitamin D deficiency may contribute to CFS/ME though association with increased oxidative stress, inflammation, and subsequent generation of fatigue symptoms.<sup>35</sup> In a series of case reports, the treatment of CFS/ME with vitamin D was reported to result in a modest clinical improvement in some individuals.<sup>36</sup> No controlled clinical trials of vitamin D in CFS/ME have occurred.

Because symptoms of severe vitamin D deficiency may include fatigue, depression, weakness, and muscle pain, people with vitamin D deficiency may often be misdiagnosed as having FM or CFS.<sup>37</sup> In one report, 93% of adults and children presenting with nonspecific muscle pain were vitamin D deficient.<sup>38</sup> Another study found that 58% of participants with musculoskeletal pain, headache, and fatigue were vitamin D deficient.<sup>39</sup> Individuals with nonspecific skeletal muscle pain should have their serum 25(OH)D assessed because of the wide-ranging health benefits of treating vitamin D deficiency.<sup>40</sup>

**Long-chain Polyunsaturated Fatty Acids.** It has been hypothesized that a functional impairment of fatty-acid metabolism may in part explain functional changes in the central nervous system as well as clinical symptoms for individuals with CFS/ME. Central to this hypothesis is the

notion that viral infection associated with CFS/ME may impair the biosynthetic pathway for long-chain polyunsaturated fatty acids (PUFAs) that in turn could have important consequences for the structure and function of the central nervous system.<sup>41</sup>

The findings of a randomized, controlled clinical trial lend support to this hypothesis.<sup>42</sup> The researchers observed that treatment with the fatty acids  $\gamma$ -linolenic acid (GLA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) improved the symptoms of CFS/ME. A second clinical trial, however, failed to confirm these results.<sup>43</sup>

In a series of case reports, treatment with high potency EPA and GLA resulted in clinical improvement for CFS/ME sufferers.<sup>44</sup> And in a separate case report, high-resolution, structural scans using magnetic resonance imaging (MRI) revealed that treatment was accompanied by improvements in brain structure—a reduction in lateral ventricular volume.<sup>45</sup>

**B Vitamins.** Functional deficiencies of the vitamins pyridoxine, riboflavin, and thiamine in individuals with CFS/ME have been reported.<sup>46</sup> And evidence of low levels of serum folate and elevated levels of homocysteine in cerebrospinal fluid—a functional marker of folate or vitamin B<sub>12</sub> deficiency—have also been documented.<sup>47,48</sup>

Studies of clinical interventions with B vitamins have been mixed. Two randomized, controlled trials have compared treatment with nicotinamide adenine dinucleotide (NADH), the active form of niacin, to treatment with a placebo or to psychological therapy. One randomized clinical trial showed statistically significant effects for NADH (10 mg) on symptom scores after 1 month of treatment, when compared with a placebo.<sup>49</sup> A second clinical trial also reported significant positive effects for NADH (5-10 mg) in the first month of treatment and a continued but modest trend toward improvement after 3 months.<sup>50</sup> Treatment with a multivitamin and minerals was found to improve symptoms of functional fatigue while another study of a multivitamin in CFS/ME sufferers demonstrated no benefit.<sup>51,52</sup> A study of a folate and vitamin B<sub>12</sub> also reported no evidence of benefit.<sup>53</sup>

**Magnesium.** Low magnesium status has been described in CFS/ME and FM sufferers in some but not all studies, and the contribution of low magnesium status to the pathogenesis of chronic fatigue remains controversial.<sup>54,55</sup> It has been suggested, however, that subclinical magnesium deficiency could be difficult to detect and could be linked to the development of CFS/ME via contribution to a pro-oxidant, low-grade inflammatory state.<sup>56</sup>

Some empirical evidence suggests that magnesium supplementation may be helpful to individuals with CFS/ME. In a case control study, intravenous treatment with magnesium was found to improve energy levels and emotional state and to reduce pain.<sup>57</sup> And an isolated case report described an individual with severe CFS/ME who experienced significant clinical improvement after intravenous magnesium therapy.<sup>58</sup>

**Amino Acids.** Based on the hypothesis that a functional deficiency in various amino acids required for neurotrans-

mitter synthesis and production of adenosine triphosphate (ATP) might contribute to CFS/ME, an exploratory open label study was conducted.<sup>59</sup> CFS/ME participants had their fasting levels of plasma amino acid measured and were then prescribed 15-gram mixtures of free-form amino acids based on their test results. The treatment duration was 3 months. Of the 20 participants who completed the study, 90% experienced at least a 25% improvement in symptoms, with 75% having reported a 50% to 100% improvement. This promising study suggests a need for further research on the potential of personalized amino acid therapy.

**Carnitine.** The amino acid carnitine plays a crucial role in mitochondrial energy production, and both functional deficiencies and the effects of dietary supplementation have been investigated. In one study, the plasma carnitine status of participants with CFS/ME was found to be 30% to 40% lower in certain forms of carnitine than controls, with a significant correlation between carnitine concentrations and clinical symptoms.<sup>60</sup>

A randomized, controlled trial of carnitine (3000 mg/d) in individuals with CFS/ME demonstrated a significant clinical improvement in symptoms, especially between the fourth and eighth week of treatment.<sup>61</sup> Comparing acetyl-L-carnitine (2000 mg/d), propionyl-L-carnitine (2000/d), or a combined treatment (2000 mg of each/d), an open label study found beneficial effects on symptoms such as fatigue, pain, and cognitive function from all treatments.<sup>62</sup>

**Zinc.** Serum zinc has been found to be significantly lower in individuals with CFS/ME versus healthy controls, and low levels of zinc have been associated with an increase in symptom severity and measures of immunological dysfunction.<sup>63</sup> Based on the correlation between low serum zinc and increased clinical symptom severity, the study's investigators suggested that some participants with CFS/ME should be considered for treatment with zinc supplements. Although no clinical trials of zinc in CFS/ME have occurred, clinical evidence suggests that zinc supplementation may influence fatigue, immune function, mood, inflammation, and oxidative stress.<sup>64-67</sup>

## PHYSICAL FITNESS

A characteristic feature of CFS/ME is worsening of symptoms after increased daily physical activity or modest amounts of exercise.<sup>68,69</sup> Individuals with CFS/ME are also known to have a lower, peak, isometric muscle strength and perform less physical activity during daily life.<sup>70</sup> Compared to healthy controls, individuals with CFS/ME tend to have a relatively lengthened and accentuated, oxidative stress response to physical activity that is linked to the development of postexertional symptom exacerbation.<sup>71</sup> Elevations in the proinflammatory, cytokine tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) at 2 time points—3 hours and 3 days after exercise—have also been observed.<sup>72</sup>

To improve physical fitness gradually and reduce symptoms, GET has been proposed as a treatment for CFS/ME and appears to be moderately effective when delivered by highly experienced therapists. A systematic review of GET

suggested that some individuals might benefit from exercise therapy.<sup>73</sup> A more recent review of GET, which examined 12 studies, concluded that consistent evidence of benefit exists, although the level of benefit was not quantifiable.<sup>74</sup> Nevertheless the role of GET has been criticized based on marginal benefits versus usual care, and opponents suggest that exercise may exacerbate an underlying pathological state of inflammatory and oxidative stress, resulting in symptom exacerbation and patients' dissatisfaction.<sup>75</sup>

Overall, the effects of GET appear to be modest and may have adverse effects.<sup>76</sup> Therefore, GET may not always be appropriate, and the underlying inflammation and oxidative stress may need to be addressed first. If commencing exercise therapy, a self-paced approach may minimize risk of adverse effects (ie, advise patients not to increase physical activity if they are well and to reduce or stop exercise if unwell).<sup>77</sup>

## PSYCHOLOGICAL AND PHYSICAL STRESS

### Stress Management

The role of stress and the functional dynamics of the hypothalamic-pituitary-adrenal (HPA) axis in the development, maintenance, and treatment of CFS/ME have attracted considerable research. Dysfunction of the HPA axis is one of the most consistent findings in CFS/ME, with evidence suggesting an influence on functional status and treatment response.<sup>78</sup>

A review of the current evidence concluded that the most generalizable characteristic of the HPA axis dysfunction across CFS/ME sufferers is a modest reduction in cortisol levels in some individuals.<sup>79</sup> Underlying, low cortisol levels are changes in HPA axis dynamics, including an attenuated, diurnal variation of cortisol; enhanced negative feedback to the HPA axis; and blunted HPA axis responsiveness.

In some cases, the development of CFS/ME may be preceded by adverse life events and neuroendocrine dysfunction.<sup>80</sup> However, it seems that HPA axis dysfunction typically develops after the onset of CFS/ME, at which point it plays an important role in the maintenance of symptoms and in the disease's course.<sup>79</sup> It has been proposed that the cause of HPA axis dysfunction is multifactorial and involves a variety of factors, including physical inactivity, diet, sleep disturbance, chronic psychological stress, mental health, and the phase of the CFS/ME itself.<sup>81</sup>

### Cognitive Behavioral Therapy

One intervention that may improve some individuals' ability to cope with the illness and modestly improve clinical symptoms is cognitive behavioral therapy (CBT).<sup>82</sup> A clinical trial of CBT found a 16% increase in total cortisol output after 6 months of therapy, making it one of the few interventions shown to improve cortisol levels in individuals with CFS/ME.<sup>83</sup> It is worth noting, however, that some individuals with CFS/ME report feeling worse after CBT, which may be due in part to deficits in clinical administration or to side effects from graded exercise usually incorporated in CBT treatment.<sup>84</sup>

## Mind-Body Medicine

Mind-body therapies may help reduce stress and improve HPA axis function. Three meditation interventions for CFS/ME have found a reduction in symptoms and/or an increase in physical functioning.<sup>85</sup> And fatigue symptoms and mental functioning improved compared to controls in a randomized, controlled trial of qigong exercise.<sup>86</sup>

## Low-dose Hydrocortisone

Because low cortisol is a common feature of CFS/ME, some studies have explored the effects of low-dose hydrocortisone administration, although this treatment is not recommended.<sup>87</sup> While low-dose hydrocortisone is generally well-tolerated and can reduce fatigue in the short term, studies of clinical interventions have suggested that treatment suppresses adrenal glucocorticoid responsiveness, which limits the usefulness of this therapy.<sup>88,89</sup>

## Herbal Adaptogens

Herbal medicines with evidence for improving physiological adaptation to stress are referred to as adaptogens.<sup>90</sup> An isolated case report suggested that treatment with the herbal medicine licorice (*Glycyrrhiza glabra*) could improve symptoms of CFS/ME.<sup>91</sup> The researcher hypothesized that this effect was due to the ability of glycyrrhetic acid, an active metabolite in licorice, to inhibit the enzymatic breakdown of cortisol. Evidence suggests that licorice can increase cortisol availability; however, it has not been studied in individuals with CFS/ME.<sup>92</sup>

The herbal medicine *Rhodiola rosea* has demonstrated an antifatigue effect in a number of clinical studies.<sup>93</sup> In individuals with stress-related burnout, *R rosea* was found to improve mood, fatigue, and HPA axis function, although investigations related to CFS/ME are lacking.<sup>94</sup>

A clinical study of Siberian ginseng (*Eleutherococcus senticosus*) failed to find overall evidence of benefit in participants with chronic fatigue; however, a subgroup analysis did suggest a modest benefit in participants with less-severe fatigue.<sup>95</sup>

## ENVIRONMENTAL POLLUTANTS

A number of reports have linked toxins—including pesticides and insecticides, mercury, lead, nickel, and ciguatera poisoning—to CFS/ME or chronic, fatigue-like symptoms.<sup>96</sup> Cadmium and tobacco smoke have also been hypothesized to play a role.<sup>97,98</sup> Because these reports are limited by several factors, such as variable exposure and outcome measurements, small sample sizes, and unreliable CFS/ME definitions, they provide only weak evidence of an association; however, further research in this area appears warranted.

In an illustrative study, serum organophosphates in CFS/ME participants were found to be higher than in control participants and comparable CFS/ME participants with a known chemical exposure.<sup>99</sup> This finding suggests a possible role for low-level bioaccumulation of persistent organic pollutants in the development of CFS/ME. Another report

found that a small group of individuals who had developed CFS/ME after toxic exposure (ciguatera poisoning or exposure to solvents) had disturbances of hypothalamic function similar to matched CFS/ME controls. Moreover, the group with toxic exposure had more severe dysfunction of the immune system.<sup>100</sup>

### Nutritional Detoxification

Various methods are available to enhance detoxification. A number of foods and nutrients have been shown to reduce absorption and/or enhance the excretion of various toxicants, while avoidance of environmental and food sources of toxins may minimize exposure.<sup>101</sup> Nutritional detoxification incorporates dietary change and the use of nutrients to support endogenous detoxification pathways and has been shown to enhance hepatic metabolism and improve subjective symptoms of fatigue.<sup>102-105</sup>

A detoxification program using ascorbic acid and choline for individuals with CFS/ME reported that symptoms improved as blood levels of pesticides decreased.<sup>106</sup> And a group of individuals with mercury toxicity and severe fatigue, but not established CFS/ME, reportedly experienced excellent improvements after specialized dental-amalgam removal (a source of mercury exposure) and a detoxification program incorporating oral dimercapto-succinic acid (DMSA), chlorella, and additional nutrient and antioxidant support.<sup>107</sup> Interestingly, infrared sauna therapy, which might support diaphoretic elimination of persistent organic pollutants, may also benefit CFS/ME.<sup>108,109</sup>

### GASTROINTESTINAL DISTURBANCES

Gastrointestinal dysfunction is very common in CFS/ME and may contribute to the pathogenesis of the disease.<sup>110</sup> A number of changes in gastrointestinal function have been identified in CFS/ME, including alterations in the gut microbiota (dysbiosis), increased gastrointestinal permeability, and altered mucosal immunity. The gastrointestinal system has also been considered a source of systemic, low-grade inflammation and oxidative stress in CFS/ME.<sup>111</sup>

In particular, dysbiosis, increased intestinal permeability, and subsequent low-grade metabolic endotoxemia, or *leaky gut*, have been suggested to play a role in CFS/ME pathogenesis.<sup>112,113</sup> Low levels of *Bifidobacterium*, high levels of *Enterococcus* and *Streptococcus*, and small intestinal bacterial overgrowth (SIBO) have been identified and may influence systemic CFS/ME pathology.<sup>114,115</sup> And compared to healthy controls, the prevalence and median values for serum antibodies against the lipopolysaccharide (endotoxin) were found to be significantly greater in participants with CFS/ME and were significantly correlated to symptom severity.<sup>116</sup>

### Nutritional Management of Leaky Gut

Circulating endotoxin has been shown to be highly responsive to dietary change, with a healthy dietary pattern able to reduce circulating endotoxin by 31% within 1 month.<sup>117</sup> One study examined the effects of a clinical

intervention aimed at reducing intestinal permeability and circulating endotoxin in CFS/ME. Dietary change and treatment with anti-inflammatory and antioxidative nutrients—such as glutamine, *N*-acetylcysteine, and zinc—over 10 to 14 months significantly reduced antibody responses to endotoxin, with over 50% of participants showing significant clinical improvement or remission.<sup>118</sup>

### Probiotics

Experimental evidence suggests that administration of probiotic bacteria may attenuate the underlying pathology of CFS/ME, namely systemic inflammation and oxidative stress.<sup>119</sup> Probiotic bacteria have also been demonstrated to influence HPA-axis function and mood in humans, which may be of particular relevance to CFS/ME sufferers.<sup>120</sup>

A clinical intervention with a strain of *Lactobacillus casei* Shirota in participants with CFS/ME was found to increase gut *Lactobacillus* and *Bifidobacterium* and to decrease anxiety symptoms significantly after 8 weeks of treatment, as compared to controls.<sup>121</sup> And another clinical trial of a probiotic (*Lactobacillus paracasei* sp. *paracasei* F19, *Lactobacillus acidophilus* NCFB 1748, and *Bifidobacterium lactis* Bb12) in CFS/ME found a significant improvement in neurocognitive function and a trend toward improvement in general symptoms and quality of life in some individuals.<sup>122</sup>

### CHRONIC INFECTION

The development of CFS/ME is frequently reported to occur after infectious-like illness characterized by symptoms such as myalgia, fever, adenopathy, and respiratory issues, and/or gastrointestinal disturbances. Several viruses and some bacteria have been implicated, although the evidence for a specific infectious cause of CFS/ME is mixed. Immune dysfunction has also been reported; in particular, impaired T- and B-cell memory and altered natural killer (NK) cell activity may decrease resistance to viral pathogens. It is likely that an interplay between decreased immunological resistance and chronic viral infection plays a role in maintaining CFS/ME symptoms.<sup>123</sup>

Many of the pathogens linked to CFS/ME are able to produce a persistent, often lifelong, infection and, therefore, may be a cause of continued immunological involvement. Several have also been shown to be neuropathogens directly or indirectly affecting the central nervous system, which may in part explain the pathological features and clinical symptoms of CFS/ME.<sup>124</sup> Further, experimental evidence suggests that viral infection may be exacerbated by chronic stress.<sup>125</sup>

A number of immunological therapies have been explored, with mixed evidence of benefit. For example, intravenous immunoglobulin therapy was found to be ineffective, while  $\alpha$ -interferon treatment improved quality of life only in individuals with low NK cell function.<sup>126,127</sup> In contrast, long-term treatment with the antiviral drug valacyclovir led to decreased serum antibodies to Epstein-Barr virus (EBV) and a significant clinical improvement in a subgroup of individuals with CFS/ME with persistent EBV infection.<sup>128</sup>

### **Immunonutrition and Herbal Medicine**

Nutritional interventions—for example, vitamin C, zinc, and essential fatty acids—have been proposed to play a role in CFS/ME management due to their potential to improve immunological function and/or act as antiviral agents; however, human clinical investigations are lacking.<sup>56</sup> Of particular note, low PUFAs and zinc status have been observed in individuals with CFS/ME and correlated with decreased immune function.<sup>129,130</sup> Both zinc and PUFAs have well documented immunomodulatory activity.<sup>131,132</sup>

An exploratory study of the herbal medicines *Echinacea* and *Panax ginseng* found that they were able to stimulate cellular immune function in the isolated serum of participants with CFS/ME.<sup>133</sup> Considering the well-established immune modulating and antiviral effects of *Echinacea*, investigation in CFS/ME sufferers with evidence of chronic viral infection appears warranted.<sup>134</sup>

### **INFLAMMATION AND OXIDATIVE STRESS**

Inflammation and oxidative stress have been proposed as fundamental pathological features of CFS/ME, and several independent investigations have found evidence of distinct elevations in chronic, low-grade inflammation and oxidative stress in CFS/ME sufferers compared to healthy controls.<sup>135-137</sup>

For example, one study found significantly increased levels of C-reactive protein (CRP) and 8-iso-prostaglandin F<sub>2α</sub> isoprostanines in participants with CFS/ME versus healthy participants.<sup>138</sup> In another investigation, peroxide concentrations were significantly higher in participants with CFS/ME and distinctly differentiated participants with CFS/ME from healthy controls.<sup>139</sup> And some evidence suggests that elevations in oxidative stress correlate directly with symptom severity.<sup>140</sup>

The elevation in inflammation and oxidative stress underlying CFS/ME has been proposed to place individuals at risk for other chronic diseases associated with these pathological sequelae; in particular, heart disease may be a risk.<sup>141</sup> Cardiovascular risk factors are higher in CFS/ME sufferers, and a lower life expectancy has been reported in individuals with CFS/ME, with heart failure a major cause of mortality.<sup>142,143</sup>

### **Antioxidant and Anti-inflammatory Nutrition**

Because oxidative stress may play an important role in disease pathogenesis and can be reduced by dietary change and nutritional supplementation, such interventions have been proposed for the management of CFS/ME but so far are not well-investigated.<sup>144</sup> Additionally the interpretation of nutritional antioxidant interventions is limited by the fact that an antioxidative function is typically only one of many diverse and unique biological effects of various nutritional substances. Nonetheless some experimental evidence in models of CFS/ME has indicated that certain natural antioxidants may result in reductions in oxidative stress that correlate with symptom improvement.<sup>145</sup> For example, both green tea extract and curcumin have been shown to reduce oxidative stress and fatigue.<sup>146,147</sup>

The dietary supplement coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>) is an essential cofactor in mitochondrial energy metabolism and a strong antioxidant with indications of potential benefit in CFS/ME. CoQ<sub>10</sub> is produced endogenously; however, a number of studies have indicated a functional deficiency of CoQ<sub>10</sub> in individuals with CFS/ME and FM that may be related to clinical symptoms, increased oxidative stress, and compromised mitochondrial energy metabolism.<sup>148-151</sup> Although CoQ<sub>10</sub> supplementation has not yet been studied in CFS/ME, a number of clinical reports concerning individuals with FM have suggested CoQ<sub>10</sub> treatment can improve symptoms, such as muscle pain, sleep, alertness, headache, and fatigue while decreasing oxidative stress and increasing the formation of new mitochondria (mitochondrial biogenesis).<sup>152-154</sup>

Inflammation can also be mitigated by nutrition. For example, the traditional Mediterranean dietary pattern has been shown to reduce chronic, low-grade inflammation and may hypothetically be of benefit in CFS/ME.<sup>155</sup> A number of dietary supplements have demonstrated anti-inflammatory effects in human clinical studies, including PUFAs and magnesium, which, as previously discussed, may have particular relevance to CFS/ME sufferers.<sup>156,157</sup>

### **MITOCHONDRIAL DYSFUNCTION**

A number of independent investigators have suggested that mitochondrial dysfunction may be central to the pathology of CFS/ME.<sup>158-161</sup> Using a test that measures the availability of ATP and the efficiency of oxidative phosphorylation in mitochondria, it was found that all tested individuals with CFS/ME had evidence of mitochondrial dysfunction, as compared to controls, and this dysfunction was correlated with the severity of the illness.<sup>162</sup> This finding is supported by other studies indicating the involvement of mitochondrial dysfunction.<sup>163-166</sup>

Evidence of CoQ<sub>10</sub> deficiency in CFS/ME provides further support for mitochondrial involvement, as CoQ<sub>10</sub> status has been proposed as a measure of mitochondrial function.<sup>167</sup> CoQ<sub>10</sub> deficiency has been shown to decrease expression of proteins involved in mitochondrial energy metabolism, reduce mitochondrial membrane potential, increase production of reactive oxygen species, and result in the degradation of dysfunctional CoQ<sub>10</sub>-deficient mitochondria.<sup>168</sup>

### **Mitochondrial Nutrition**

Mitochondrial nutrients have been defined as nutritional compounds that (1) enter the cells and mitochondria following exogenous administration, (2) protect the mitochondria from oxidative damage, and (3) improve mitochondrial function.<sup>169</sup> A number of important effects have been ascribed to various mitochondrial nutrients, including the ability to reduce oxidative stress, enhance energy metabolism, and increase mitochondrial biogenesis.<sup>170</sup>

The clinical effects of a number of nutrients discussed above may be due in part to improvements in mitochondrial function. For example, high doses of B vitamins can stimu-

**Table 1.** Functional Pathology Assessment Methods Relevant to CFS/ME

Area of Investigation	Functional Assessments	Discussion
<b>Diet and nutritional status</b>	<ul style="list-style-type: none"> <li>• Nutritional/functional deficiencies:                             <ul style="list-style-type: none"> <li>– Vitamin D</li> <li>– Fatty acids</li> <li>– Magnesium</li> <li>– Zinc</li> <li>– Carnitine</li> <li>– B vitamins</li> </ul> </li> <li>• Gluten sensitivity/celiac disease</li> <li>• Food sensitivity profile (IgG)</li> </ul>	<ul style="list-style-type: none"> <li>• Identification of nutritional deficiencies could individualize treatment.</li> <li>• The possibility of celiac disease can be explored with IgA antitissue transglutaminase antibodies.<sup>171</sup></li> <li>• IgG testing can be used to structure an elimination diet.<sup>172</sup></li> </ul>
<b>HPA axis dysfunction</b>	<ul style="list-style-type: none"> <li>• Salivary cortisol/DHEA (waking, diurnal)</li> </ul>	<ul style="list-style-type: none"> <li>• Salivary cortisol is a sensitive measure of dynamic HPA axis activity and diurnal and/or waking cortisol and can be used assesses cortisol output.<sup>173-175</sup></li> </ul>
<b>Environmental toxicity</b>	<ul style="list-style-type: none"> <li>• Provoked urinary excretion challenge</li> <li>• Serum, persistent organic pollutants</li> </ul>	<ul style="list-style-type: none"> <li>• Available testing methods may underestimate total body burden of environmental pollutants; however, provoked urinary excretion challenge for toxic metals and serum persistent organic pollutants are clinically useful.<sup>176,177</sup></li> </ul>
<b>Gastrointestinal function</b>	<ul style="list-style-type: none"> <li>• Comprehensive stool microbiology</li> <li>• SIBO</li> <li>• Intestinal permeability (lactulose/mannitol)</li> </ul>	<ul style="list-style-type: none"> <li>• Assessment of gut ecology and small intestinal bacterial overgrowth can help identify dysbiosis.<sup>178,179</sup></li> <li>• Because endotoxin is not easily measured in a clinical setting, the lactulose mannitol test may act as an indicator of leaky gut and elevated blood endotoxin.<sup>180</sup></li> </ul>
<b>Chronic viral infection</b>	<ul style="list-style-type: none"> <li>• Chronic viral disease evaluation (eg, Epstein-Barr virus, herpes virus, cytomegalovirus)</li> </ul>	<ul style="list-style-type: none"> <li>• If infection is a suspected disease trigger a viral disease evaluation should be undertaken.<sup>10</sup></li> </ul>
<b>Oxidative stress</b>	<ul style="list-style-type: none"> <li>• Biomarkers of oxidative stress (eg, F<sub>2</sub>-isoprostanes)</li> </ul>	<ul style="list-style-type: none"> <li>• F<sub>2</sub>-isoprostanes in blood or urine are widely regarded a reliable reference marker for oxidative stress.<sup>181</sup></li> </ul>
<b>Inflammation</b>	<ul style="list-style-type: none"> <li>• hs-CRP</li> </ul>	<ul style="list-style-type: none"> <li>• hs-CRP is a sensitive marker of low-grade inflammation and could also be used to assess associated cardiovascular disease risk.<sup>182</sup></li> </ul>
<b>Mitochondrial function</b>	<ul style="list-style-type: none"> <li>• Urinary organic acids</li> <li>• Serum CoQ<sub>10</sub></li> </ul>	<ul style="list-style-type: none"> <li>• Urinary organic acids may help identify impaired mitochondrial energy production and functional deficiencies in mitochondrial nutrients.<sup>183</sup></li> <li>• Serum CoQ<sub>10</sub> is a proposed biomarker of mitochondrial dysfunction.<sup>143</sup></li> </ul>

Abbreviations: IgG = immunoglobulin G; SIBO = small intestinal bacterial overgrowth; DHEA = dehydroepiandrosterone; HPA = hypothalamic-pituitary-adrenal; hs-CRP = high sensitivity C-reactive protein (hs-CRP); CoQ<sub>10</sub> = coenzyme Q<sub>10</sub>.

late defective coenzymes; magnesium is a cofactor in ATP metabolism; and acetyl-L-carnitine is responsible for the transport of acetyl-CoA into the mitochondria during fatty acid oxidation.<sup>184-186</sup> An open-label study with D-ribose, a structural component of intermediate metabolites required for mitochondrial energy metabolism, found significant improvements in energy, well-being, sleep, and mental clarity and decreased pain in a group of participants with CFS/ME and FM after 3 weeks.<sup>187</sup> And investigation of a nutritional formulation designed to support mitochondrial function—containing vitamins, minerals, amino acids, plant extracts, phospholipids, and fatty acids—reported a 43% reduction in fatigue in individuals with CFS/ME and FM after 8 weeks of treatment.<sup>188</sup>

Preliminary findings from a clinical audit of CFS/ME individuals who showed evidence of mitochondrial dysfunction and who had received an integrative treatment plan, suggested that this approach may result in important improvements in clinical symptoms and mitochondrial function.<sup>189</sup> This plan frequently included the mitochondrial nutrients D-ribose, magnesium, acetyl-L-carnitine, and CoQ<sub>10</sub>.

## DISCUSSION

The possible causes, disordered physiology, and clinical presentations of CFS/ME vary between individuals. For example not all individuals may have vitamin D deficiency, low diurnal cortisol, or active EBV infection. An integrative management approach could help identify an individual's unique state of dysfunction and personalize treatment. Clinical assessment might therefore use investigative methods that help delineate functional status (ie, functional pathology); see Table 1.

The assessment of the unique functional status of an individual may help identify treatments that are more likely to elicit a clinical response. Personalization of treatments may be particularly relevant to nutritional interventions where background nutritional status may influence therapeutic effect. This comprehensive approach could be very useful in the clinical practice to get symptom relief for one unique individual at a time.

Relevant to future CFS/ME research, this approach is evidently different from clinical trials that evaluate single interventions across broad groups of participants. Methodology would need to be developed that takes into account subgroups of participants, individualized assessments, and tailored treatment plans.

Finally, an integrative management model may increase the cost and commitment to treatment; however, it is likely to produce better outcomes by addressing the fundamental pathological features as well as environmental, lifestyle, and behavioral factors that contribute to the maintenance of the disease.

## CONCLUSION

Currently accepted treatments for CFS/ME have modest clinical benefits and for most patients the disease prognosis

remains poor. Because CFS/ME is a heterogeneous disorder with diverse etiological factors and pathological features, a patient-centered integrative framework based on modifiable physiological and environmental factors may offer hope for more effective management and better clinical outcomes. An individualized approach to patient management may also help identify patient subgroups that are more likely to respond favorably to specific treatments. A personalized, integrative approach to CFS/ME deserves further consideration as a template for patient management and future research.

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