

Mitochondrial Dysfunction and Chronic Disease: Treatment With Natural Supplements

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Abstract

Loss of function in mitochondria, the key organelle responsible for cellular energy production, can result in the excess fatigue and other symptoms that are common complaints in almost every chronic disease. At the molecular level, a reduction in mitochondrial function occurs as a result of the following changes: (1) a loss of maintenance of the electrical and chemical transmembrane potential of the inner mitochondrial membrane, (2) alterations in the function of the electron transport chain, or (3) a reduction in the transport of critical metabolites into mitochondria. In turn, these changes result in a reduced efficiency of oxidative phosphorylation and a reduction in production of adenosine-5'-tri-

phosphate (ATP). Several components of this system require routine replacement, and this need can be facilitated with natural supplements. Clinical trials have shown the utility of using oral replacement supplements, such as L-carnitine, alpha-lipoic acid (α -lipoic acid [1,2-dithiolane-3-pentanoic acid]), coenzyme Q₁₀ (CoQ₁₀ [ubiquinone]), reduced nicotinamide adenine dinucleotide (NADH), membrane phospholipids, and other supplements. Combinations of these supplements can reduce significantly the fatigue and other symptoms associated with chronic disease and can naturally restore mitochondrial function, even in long-term patients with intractable fatigue.

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Mitochondrial dysfunction, characterized by a loss of efficiency in the electron transport chain and reductions in the synthesis of high-energy molecules, such as adenosine-5'-triphosphate (ATP), is a characteristic of aging, and essentially, of all chronic diseases.¹⁻⁴ These diseases include neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Friedreich's ataxia^{1,2,4,5}; cardiovascular diseases, such as atherosclerosis and other heart and vascular conditions^{6,7}; diabetes and metabolic syndrome⁸⁻¹⁰; autoimmune diseases, such as multiple sclerosis, systemic lupus erythematosus, and type 1 diabetes¹¹⁻¹⁴; neurobehavioral and psychiatric diseases, such as autism spectrum

disorders, schizophrenia, and bipolar and mood disorders¹⁵⁻¹⁹; gastrointestinal disorders^{20,21}; fatiguing illnesses, such as chronic fatigue syndrome and Gulf War illnesses²²⁻²⁴; musculoskeletal diseases, such as fibromyalgia and skeletal muscle hypertrophy/atrophy²⁵⁻²⁷; cancer^{28,29}; and chronic infections.^{30,31}

It is well known among researchers that mitochondrial genetic or primary mitochondrial disorders contribute to mitochondrial dysfunction and secondary or acquired degenerative disorders.³² This review will concentrate on nongenetic or acquired mechanisms that could explain mitochondrial dysfunction and their replacement treatment with natural supplements and combinations of natural supplements, including vitamins, minerals, enzyme cofactors, antioxidants, metabolites, transporters, membrane-type phospholipids, and other natural supplements.

Mitochondrial Molecular Dysfunction

Mitochondrial dysfunction arises from an inadequate number of mitochondria, an inability to provide necessary substrates to mitochondria, or a dysfunction in their electron transport and ATP-synthesis machinery. The number and functional status of mitochondria in a cell can

be changed by (1) fusion of partially dysfunctional mitochondria and mixing of their undamaged components to improve overall function, (2) the generation of entirely new mitochondria (fission), and (3) the removal and complete degradation of dysfunctional mitochondria (mitophagy).³³ These events are controlled by complex cellular processes that sense the deterioration of mitochondria, such as the depolarization of mitochondrial membranes or the activation of certain transcription pathways.^{34,35}

The ability of cells to produce almost all high-energy molecules such as ATP is directly related to the ability of mitochondria to (1) convert the energy of metabolites to reduced nicotinamide adenine dinucleotide (NADH) and (2) transfer electrons from NADH to the electron transport chain and eventually to molecular oxygen while pumping protons from the mitochondrial matrix across the inner mitochondrial membrane to the intermembrane space. This process creates a transmembrane proton gradient (Δp) and an electrochemical gradient ($\Delta \Psi_m$) across the mitochondrial inner membrane.^{36,37} The transmembrane potential created by the proton gradient then uses ATP synthase to flow protons back across the inner mitochondrial membrane and employs the energy from this process to drive adenosine diphosphate (ADP) phosphorylation to ATP.^{36,38}

A consequence of the electron transport process is the production of reactive oxygen species (ROS), highly reactive free radicals that are produced as a by-product of oxidative phosphorylation. The main sources of ROS and the related reactive nitrogen species (RNS) are mitochondria, and these free radicals can damage cellular lipids, proteins, and DNA.³⁹⁻⁴¹ However, some mechanisms can neutralize ROS/RNS; dismutase enzymes and antioxidants can control excess amounts of ROS/RNS.^{42,43} In addition to creation of ROS/RNS, the electron transport process can induce uncoupling proteins, resulting in a controlled leak of protons back across the proton gradient of the inner mitochondrial membrane into the mitochondrial matrix.^{36,37} This leak results in reduced ATP production while it still consumes excess oxygen.⁴³

In the presence of a controlled proton leak, excess oxygen consumption and the resulting ROS production can result in inappropriate damage to mitochondrial membrane lipids,^{41,42} such as the very ROS/RNS-sensitive cardiolipin, an inner mitochondrial membrane phospholipid.⁴⁴ Oxidative damage to the cardiolipin and other membrane phospholipids in the inner mitochondrial membrane can result in increased proton and ion leakage back across the inner membrane into the mitochondrial matrix and partial loss of the electrochemical gradient. Cardiolipin is also an important component of the electron transport chain, providing stability for the cytochrome/enzyme complexes in the inner mitochondrial membrane.⁴⁴ Once adversely damaged by ROS/RNS, oxidized cardiolipin instigates loss of electron-transport function.⁴⁵

Cellular antioxidant defenses usually maintain ROS/RNS levels at concentrations that prevent excess oxidation of cellular molecules.⁴⁶⁻⁴⁸ Cellular antioxidant defenses that are endogenous are mediated by glutathione peroxidase, catalase, and superoxide dismutase, among other enzymes.^{48,49} Also, some dietary antioxidants with a low molecular weight can affect antioxidant status.^{50,51} Some of these dietary antioxidants have been used as natural preventive agents to shift the excess concentrations of oxidative molecules down to physiological levels that can be maintained by endogenous antioxidant systems.⁵²

Mitochondrial Dysfunction and Fatigue

Mitochondrial dysfunction is directly related to excess fatigue. Fatigue is considered a multidimensional sensation that is perceived to be a loss of overall energy and an inability to perform even simple tasks without exertion.^{53,54} Although mild fatigue can be caused by a number of conditions, including depression and other psychological conditions, moderate to severe fatigue involves cellular energy systems.^{53,54} At the cellular level, moderate to severe fatigue is related to loss of mitochondrial function and diminished production of ATP.⁵⁴⁻⁵⁶ Intractable fatigue lasting more than 6 months that is not reversed by sleep (chronic fatigue) is the most common complaint of patients seeking general medical care.^{53,57} Chronic fatigue is also an important secondary condition in many clinical diagnoses, often preceding patients' primary diagnoses.^{57,58}

As a result of aging and chronic diseases, oxidative damage to mitochondrial membranes impairs mitochondrial function.⁵⁹⁻⁶¹ As an example, individuals with chronic fatigue syndrome present with evidence of oxidative damage to DNA and lipids,^{61,62} such as oxidized blood markers⁶³ and oxidized membrane lipids,⁶⁴ that is indicative of excess oxidative stress. These individuals also have sustained, elevated levels of peroxynitrite caused by excess nitric oxide, which can also result in lipid peroxidation and loss of mitochondrial function as well as changes in cytokine levels that exert a positive feedback on nitric oxide production.⁶⁵

Natural Supplements and Mitochondrial Dysfunction

A number of natural supplements have been used to treat nonpsychological fatigue and mitochondrial dysfunction.^{32,54,66} These supplements include those containing vitamins, minerals, antioxidants, metabolites, enzyme inhibitors and cofactors, mitochondrial transporters, herbs, and membrane phospholipids (Table 1).³² Although several natural supplements have been used to reduce fatigue, few are considered truly effective.⁶⁷ This article will discuss some of the most promising supplements and conclude with combinations of specific supplements that have been used to treat intractable chronic fatigue and improve mitochondrial function.

Table 1. An Incomplete List of Ingredients/Agents That Medical Practitioners Have Used or Suggested for Treatment of Mitochondrial Dysfunction^a

Category	Examples
Vitamins	Vitamins C, D and E, thiamine, riboflavin
Minerals	Magnesium, calcium, phosphate
Lipids	Membrane phospholipids, unsaturated fatty acids
Metabolites	Creatine, pyruvate
Cofactors	CoQ ₁₀ , α-lipoic acid, NADH, nicotinic acid
Transporters	L-Carnitine, membrane phospholipids
Antioxidants	CoQ ₁₀ , α-lipoic acid, NADH, glutathione
Enzyme inhibitors	α-Lipoic acid, dichloroacetate
Herbs	Curcumin, schisandrin

Abbreviations: NADH = reduced nicotinamide adenine dinucleotide; CoQ₁₀ = coenzyme Q₁₀ (ubiquinone); α-lipoic acid = alpha-lipoic acid.

^aModified from Kerr.³²

α-Lipoic Acid

Alpha-lipoic acid (α-lipoic acid [1,2-dithiolane-3-pentanoic acid]) is a potent antioxidant, transition metal ion chelator, redox transcription regulator, and anti-inflammatory agent.⁶⁸ It acts as a critical cofactor in mitochondrial α-keto acid dehydrogenases, and thus it is important in mitochondrial, oxidative-decarboxylation reactions.^{69,70} Clinically, α-lipoic acid has been used as an oral supplement in the treatment of complications associated with diabetes mellitus, and according to a review by Shay et al,⁷⁰ it has been shown to bring about improvements in various diabetes-associated neuropathies, inflammation, and vascular health. In model cellular systems, these effects have been attributed mainly to α-lipoic acid having signal-transduction effects on gene regulation and on glucose uptake and metabolism as well as its antioxidant effects.⁷¹

As a result of aging and in many chronic diseases, certain sphingolipids—especially ceramides, and in particular, short-chain ceramides—accumulate in mitochondria due to hydrolysis of sphingomyelin by sphingomyelinase, and eventually, this accumulation

retards electron transport activity.^{72,73} Ceramide accumulation in mitochondria is particularly damaging to cardiac tissue. In aging rodents, α-lipoic acid has been used to lower ceramide levels in vascular endothelial cells of cardiac muscle through inhibition of sphingomyelinase activity, resulting in restoration of mitochondrial glutathione levels and increasing electron transport function.⁷⁴

As mentioned above, in diabetes, α-lipoic acid has been used extensively to reduce diabetic complications, such as sensorimotor polyneuropathies.⁷⁵ One 4-year, blinded study demonstrated that some neuropathic impairments improved significantly on α-lipoic acid (but not nerve conduction attributes), showing the antioxidant's clinical utility and the safety of long-term treatment with α-lipoic acid for diabetic patients.⁷⁶

Given as an oral supplement, α-lipoic acid is rarely present in tissues above micromolar levels; thus, it is unlikely to be directly involved as an important primary cellular antioxidant.⁷⁰ However, its ability to increase cellular glutathione levels is an important antioxidant property, and this increase is accomplished by regulating glutathione synthesis and thus ameliorating oxidative stress.⁷⁷ This antioxidant can affect the regulation of the nuclear transcription factor NF-κB, and, thus, it can cause widespread transcriptional effects, resulting in the attenuation of production of free radicals and cytotoxic cytokines.⁷⁸

As a transition metal chelator, α-lipoic acid can remove excess copper, iron, and other metals that are involved in chronic diseases, such as hemochromatosis, end-stage renal failure, and Alzheimer's and Parkinson's diseases, and it is a potential therapeutic agent for prevention or mitigation of heavy metal poisoning.⁶⁸ It also improves cognitive function and mitochondrial function, suggesting a link between oxidative damage to mitochondria and cognition.⁷⁹ The use of α-lipoic acid for chronic fatigue has not yet been studied in controlled clinical trials, but its widespread use as a safe supplement (usually 200-600 mg/d)⁷⁰ to support mitochondrial function and reduce oxidative stress has justified its incorporation into various supplement mixtures.^{70,76,78}

L-Carnitine

L-carnitine (3-hydroxy-4-N-trimethylaminobutyrate) is a naturally occurring fatty acid transporter found in all species of mammals. It is directly involved in the transport of fatty acids into the mitochondrial matrix for subsequent β-oxidation, but it also functions in removal of excess acyl groups from the body and in the modulation of intracellular coenzyme A (CoA) homeostasis.^{80,81} Because of its importance in fatty acid oxidation and CoA and acyl-CoA homeostasis, L-carnitine is usually maintained within relatively narrow concentration limits; thus, dietary supplementation is important to maintain optional L-carnitine concentrations within cells.⁸¹ Indeed, L-carnitine deficiency disorders are associated with reduced mitochondrial function, insulin resistance, and coronary artery disease.⁸²⁻⁸⁴

The important role of L-carnitine in mitochondrial metabolism has spurred the use of L-carnitine supplements to potentially improve physical performance.⁸⁵ The rationale is that increased reliance on fat as the principle substrate for energy production during extreme exercise should reduce the need for carbohydrates and delay the depletion of carbohydrate stores and that these changes should increase overall energy production and reduce exercise-induced fatigue. Transport of fatty acids into mitochondria also requires increased levels of L-carnitine, and, thus, indicates a need for dietary supplementation of L-carnitine. However, studies have shown that increasing oral L-carnitine supplementation, even for 2 to 3 weeks prior to extreme exercise, did not increase carnitine content in skeletal muscle. Therefore, it is unlikely that this supplementation alters muscle metabolism during extreme exercise.^{86,87}

L-carnitine supplementation has been successfully used in clinical disorders that are characterized by low concentrations of L-carnitine or impaired fatty acid oxidation, such as diabetes, sepsis, renal disease, and cardiomyopathy.⁸⁰ For example, in a small study of 18 individuals with congestive heart failure and 12 placebo controls, propionyl-L-carnitine supplementation resulted in increased peak heart rate (mean of 12%), exercise capacity (mean of 21%), and peak oxygen consumption (mean of 45%) in the treatment group.⁸⁸

An important antiaging use of L-carnitine has been to increase the rate of mitochondrial oxidative phosphorylation that naturally declines as a result of aging. This decline impairs energy production while it increases production of ROS/RNS. Feeding old rats acetyl-L-carnitine was found to reverse age-related decreases in L-carnitine levels while it increased fatty acid metabolism. It also reversed the age-related decline in cellular glutathione levels and improved the complex IV activity of muscle mitochondria.⁸⁹

Although dietary supplementation with L-carnitine and its various derivatives appears to be safe (doses up to 2 g/d)⁹⁰ and potentially useful in increasing mitochondrial function, researchers have not performed the necessary multiple clinical trials to show its effectiveness in most age-related chronic illnesses (other than diabetes and cardiovascular diseases). One exception was a randomized, controlled clinical trial on 70 centenarians who were treated with L-carnitine for 6 months. These participants were generally found to have muscle weakness, decreasing mental health, impaired mobility, and poor endurance. By the end of the study, the treated group showed significant improvements in physical fatigue, mental fatigue, and fatigue severity. They also showed reductions in total fat mass, increased muscle mass, and an increased capacity for physical and cognitive activity through reduced fatigue and improved cognitive function.⁹¹ Other trials on alcoholism, hepatic encephalopathy, coronary heart diseases, Peyronie's disease, cerebral ischemia, and infertility indicated that administration of L-carnitine can have positive effects on signs and symptoms of these conditions.⁹⁰

Coenzyme Q₁₀

Coenzyme Q₁₀ (CoQ₁₀ [ubiquinone]) is a key cofactor and component of the mitochondrial electron transport chain and one of the most widely used natural supplements.^{32,92} It is also a strong antioxidant in its reduced form, and it can affect the expression of certain genes involved in cell signaling, metabolism, and transport.^{92,93} However, the main role of CoQ₁₀ is its involvement in the transfer of electrons along the multiple complexes of the mitochondrial electron transport chain.^{92,94} Clinically, it has been used in doses up to 1200 mg per day, but most studies used lower doses.⁹²

Because CoQ₁₀ is an important component of the mitochondrial oxidative phosphorylation system, its supplementation in individuals with reduced levels should result in increased energy production and reduced fatigue.^{92,94} A systematic review of the effects of CoQ₁₀ in physical exercise, hypertension, and heart failure by Rosenfeldt et al⁹⁵ revealed that 6 out of 11 published studies showed modest improvements in exercise capacity in the participants given dietary CoQ₁₀. In 8 of the studies, which examined the effects of CoQ₁₀ on hypertension, a mean decrease occurred in blood pressure: systolic, a mean decline of 16 mm Hg; and diastolic, a mean decline of 10 mm Hg. In the review, 9 randomized trials that examined the use of CoQ₁₀ in participants with heart failure showed nonsignificant trends toward increased injection fraction and reduced mortality. Rosenfeldt et al⁹⁵ performed their own 3-month, randomized, placebo-controlled trial on the effects of oral CoQ₁₀ in 35 patients with heart failure and found that participants in the CoQ₁₀ arm, but not in the control arm, showed significant improvements in symptoms.⁹⁵ The study also showed a trend toward improvements in mean exercise times.⁹⁵

The effects of administration of oral CoQ₁₀ during physical exercise have also been examined. In a blinded, crossover trial, 17 healthy participants received CoQ₁₀ or a placebo for 8 days, and their performance was then evaluated twice at fixed workloads on a bicycle ergometer for 2 hours, with a 4-hour rest between the tests.⁹⁶ The participants on CoQ₁₀ were able to achieve higher work outputs and had less fatigue sensations, and their need for a recovery period was alleviated compared to the placebo group.⁹⁶

Clinically, CoQ₁₀ has been used to reduce symptoms and progression in various neurodegenerative diseases.^{92,94} In studies using Alzheimer's disease models, CoQ₁₀ administration significantly delayed brain atrophy and typical β -amyloid-plaque pathology.^{97,98} In a randomized, placebo-controlled, 16-week clinical trial on 98 Alzheimer's participants who took an oral mixture of CoQ₁₀, vitamins C and E, and α -lipoic acid, the test arm showed significant reductions in oxidative-stress markers but did not show significant changes in cerebrospinal fluid (CSF) markers related to β -amyloid or tau pathology.⁹⁹

In Parkinson's disease, individuals generally show increased oxidized-to-total CoQ₁₀ ratios and significant

increases in markers of oxidative damage in the CSF, which can be partially reversed with CoQ₁₀ administration.¹⁰⁰ In individuals with early Huntington's disease, the Huntington Study Group's trial showed that CoQ₁₀ administration for 30 months slowed the usual decline in total functional capacity, but the differences did not reach statistical significance.¹⁰¹ Finally, in a multicenter, placebo-controlled, phase II trial with amyotrophic lateral-sclerosis patients, CoQ₁₀ did not significantly modify functional decline over a 9-month period,¹⁰² and Mathews et al¹⁰³ did not find CoQ₁₀ plus several vitamins to be effective in individuals with genetic mitochondrial diseases.

Nicotinamide Adenine Dinucleotide

NADH functions as a cellular redox cofactor in over 200 cellular redox reactions and as substrate for certain enzymes.^{104,105} Humans universally require NADH, and its deficiency results in pellagra, which is characterized by dermatitis, diarrhea, dementia, and eventually death.¹⁰⁴ In the mitochondria, NADH delivers electrons from metabolite hydrolysis to the electron transport chain, but in its reduced form, it can also act as a strong antioxidant. The usual route of dietary supplementation has historically been via NADH precursors, such as niacin, nicotinic acid, or nicotinamide, but recently, microcarriers have been used to stabilize oral NADH so that it can be directly ingested in small doses and absorbed in the gastrointestinal system. This supplementation turns out to be more effective than large oral doses of NADH, as in some studies that used up to 50 mg/kg/d. At that size of dose, the NADH is prone to oxidation and degradation, and such supplementation is generally considered to be ineffective.¹⁰⁶

In neurodegenerative diseases, oxidative damage is extensive,^{1,2} and various mitochondrial antioxidants have been used to treat disease and delay progression.^{1-6,32} In Alzheimer's disease, one study showed that stabilized oral NADH could improve cognitive functioning and dementia¹⁰⁶; however, another clinical trial showed no evidence of improvements in cognition or dementia using oral NADH.¹⁰⁷ In a controlled trial with 26 Alzheimer's participants who were given stabilized NADH or placebo for 6 months, Dermin et al¹⁰⁸ found that that the test group had significantly better performance scores than the placebo group in verbal fluency and visual construction and showed a trend toward increased performance on abstract verbal reasoning. However, the study provided no evidence of better performance for measures of attention or memory or on scores of dementia severity.

Stabilized, oral NADH has also been used to ameliorate the symptoms of Parkinson's disease. In a preliminary, open-label clinical trial, Birkmayer et al¹⁰⁹ examined the effects of IV and oral NADH in over 800 individuals with Parkinson's disease. They found that 19.3% of participants showed a 30% to 50% decrease in disability; 58.8% had moderate (10%-30%) improvement; and 21.8% did not respond to the therapy ($P < .01$).

Younger patients with a shorter duration of disease had a much better chance of responding and showing more significant improvements than older patients or patients with a longer duration of disease. The oral form was comparable to IV NADH in its effects.¹⁰⁹ When they repeated this type of trial, however, Dizdar et al¹¹⁰ did not find statistically significant improvements in Parkinson's disease rating scores in participants treated with NADH, and differences were also not found in CSF clinical markers associated with Parkinson's disease severity.

Stabilized, oral NADH has also been used to reduce symptoms in patients with chronic fatigue. One such study on individuals with chronic fatigue syndrome was designed to treat participants with stabilized, oral NADH or placebo for 4 weeks in a crossover trial.¹¹¹ Of these participants, 8 of 26 (30.7%) responded positively to the microencapsulated NADH compared with 2 of 26 (8%) in the placebo arm ($P < .05$).¹¹¹ Clearly an effect occurred but only in a subset of participants in the trial; thus, these results were not considered significant by others.¹¹² A clinical trial that compared oral, stabilized NADH to psychological/nutritional therapy for 31 individuals with chronic fatigue syndrome revealed that stabilized NADH alone reduced fatigue in the first 4 months of a 12-month trial. After the first 4 months, however, symptom scores were similar in the 2 arms of the trial.¹¹³ In another study, stabilized NADH was given orally for 2 months to treat individuals with chronic fatigue syndrome.¹¹⁴ This treatment resulted in decreases in anxiety and in maximum heart rate after a stress test, but Alegre et al¹¹⁴ found few or no differences in the functional impact on fatigue, quality of life, sleep quality, exercise capacity, or functional reserve. Thus stabilized NADH alone has shown mixed results in various diseases and disorders, and not every patient responded to the oral, stabilized supplement.

Membrane Phospholipids

The dietary replacement of mitochondrial membrane phospholipids (lipid replacement therapy [LRT]) using food-derived molecules to remove damaged, mainly oxidized, membrane lipids in mitochondria and other cellular organelles has proved very effective at increasing mitochondrial function and reducing fatigue.^{10,23,54,55} To some degree, antioxidant supplements can reduce ROS/RNS levels and prevent some oxidation of mitochondrial membrane phospholipids, but antioxidants alone cannot repair the damage already done to cells, and in particular, to cells' mitochondrial inner membranes.^{29,55,115}

The use of oral membrane phospholipids plus antioxidants in doses ranging from 500 to 2000 mg per day has been effective in the treatment of certain clinical conditions, such as chronic fatigue and fatiguing illnesses.^{55,67,115-117} LRT results in the actual replacement of damaged membrane phospholipids with undamaged (unoxidized) lipids to ensure proper function of cellular and particularly mitochondrial membranes.

Table 2. Oral Membrane Phospholipid Supplementation and Fatigue in Chronically Ill Patients^a

Participants/Patients	n	Avg Age	Avg Time on LRT	PFS Fatigue Reduction (%)	Reference
Chronic fatigue	34	50.3	8 wk	40.5 ^c	Ellithorpe et al ¹¹⁷
Aging, chronic fatigue	20	68.9	12 wk	35.5 ^b	Agadjanyan et al ⁵⁵
Chronic fatigue syndrome (and/or fibromyalgia syndrome)	15	44.8	8 wk	43.1 ^b	Nicolson & Ellithorpe ¹¹⁶
Aging, fatigue	67	57.3	1 wk	36.8 ^b	Nicolson et al ¹¹⁸
Chronic illnesses	58	55.0	8 wk	30.7 ^b	Nicolson et al ¹¹⁹

Abbreviations: Avg = average; LRT = lipid replacement therapy; PFS = Piper Fatigue Scale.

^aModified from Nicolson and Settineri.⁵⁴

^b $P < .001$ compared to no supplement.

^c $P < .0001$ compared to no supplement.

Oral membrane phospholipids can increase mitochondrial function and decrease fatigue in chronic fatigue syndrome, fibromyalgia syndrome, and other fatiguing conditions, including natural aging (Table 2). For example, a mixture of membrane phospholipids and vitamins (Propax with NT Factor) was used by Ellithorpe et al¹¹⁷ in a study on aging individuals with severe chronic fatigue and was found to reduce their fatigue by 40.5% in 8 weeks. In these studies, fatigue was monitored using the Piper Fatigue Scale (PFS) to measure clinical fatigue and quality of life.⁵⁸ In a subsequent crossover study, the effects of membrane phospholipids on fatigue and mitochondrial function in patients with moderate-to-severe, chronic fatigue was initiated.⁵⁵ Oral administration of NT Factor for 12 weeks resulted in a 35.5% reduction in fatigue and 26.8% increase in mitochondrial function, whereas after a 12-week washout period, fatigue increased and mitochondrial function decreased back toward control levels.⁵⁵ Similar findings on fatigue reduction were observed in individuals with chronic fatigue syndrome and fibromyalgia syndrome who were given oral membrane phospholipids (NT Factor).¹¹⁶ Using a new formulation of NT Factor plus vitamins, minerals, and other supplements in individuals with moderate chronic fatigue resulted in a 36.8% reduction in fatigue within 1 week (Table 2).¹¹⁸

Combination Oral Supplement to Reduce Fatigue

In a 2-month trial of the treatment of long-term intractable fatigue in patients with a variety of diagnoses, the author and several colleagues combined membrane phospholipids (2000 mg/d), CoQ₁₀ (35 mg/d), microencapsulated NADH (35 mg/d), L-carnitine (160 mg/d), α -ketoglutaric acid (180 mg/d), and other nutrients into an oral supplement (ATP Fuel) to treat fatigue and mitochondrial dysfunction.^{119,120} The 58 participants in this trial had moderate-to-severe, intractable fatigue for an average of >17 years and had been to an

average of >15 practitioners without resolution of their fatigue. The study included 30 individuals with chronic fatigue syndrome; 17 with chronic Lyme disease; 16 with other fatiguing illnesses, including fibromyalgia syndrome and Gulf War illness; 4 with autoimmune disease, including rheumatoid arthritis; 2 with cancer; and 2 with diabetes. These patients had tried many drugs and supplements (average >35) to reduce their fatigue without success.

Participants in this trial took the combination LRT supplement (ATP Fuel) for 8 weeks, and fatigue was scored using the PFS.¹¹⁹ The PFS is a validated instrument that measures four dimensions of subjective fatigue: behavioral/severity, affective/meaning, sensory, and cognitive/mood.⁵⁸ The study used the instrument to calculate the four subscale or dimensional scores and the total fatigue scores. Participants had initial, total, mean PFS fatigue scores of 7.51 ± 0.29 , and after 8 weeks of supplements, the mean scores improved to 5.21 ± 0.28 , or a 30.7% reduction in fatigue (t test, $P < .0001$; Wilcoxon signed-rank, $P < .0001$).¹¹⁹

PFS scores can be further dissected into 4 subcategories: (1) the behavior/severity subcategory, which deals with completing tasks, socializing, and engaging in sexual and other activities and with intensity or degree of fatigue; (2) the affective/meaning subcategory, which determines whether an individual finds the fatigue/tiredness to be pleasant or unpleasant, agreeable or disagreeable, protective or destructive, and normal or abnormal; (3) the sensory subcategory, which determines whether an individual feels strong or weak, awake or sleepy, refreshed or tired, and energetic or unenergetic; and (4) the cognitive/mood subcategory, which assesses whether an individual feels relaxed or tense, exhilarated or depressed, and able or unable to concentrate, remember, and think clearly. In the study being discussed in this section, all of these subcategories showed significant reductions by the end of the 8-week trial ($P < .0001$),

indicating that significant improvements occurred for all subcategories of fatigue. For example, a 30.7% reduction ($P < .0001$) in severity/behavior of fatigue occurred, indicating a significant reduction in the intensity of fatigue and a significant increase in the ability to complete tasks, socialize, and engage in sexual and other activities. Also, a 28.0% improvement ($P < .0001$) occurred in mood and cognitive ability, such as the ability to concentrate, remember, and think clearly.¹¹⁹

Regression Analysis of Fatigue Data

To determine the trends in fatigue reduction as the result of participants' use of the combination LRT supplement (membrane phospholipids, CoQ₁₀, NADH, L-carnitine, α -ketoglutaric acid, and other ingredients) over the time of the trial, the author and colleagues conducted regression analyses of the data to determine if results were (1) consistent, (2) occurred with a high degree of confidence, and (3) could predict further reductions in fatigue.¹¹⁹ The regression analysis of overall fatigue and of each of the subcategories of fatigue indicated significant and consistent downward trends in the fatigue data, suggesting that further reductions in fatigue would have been likely if the trial had been continued. The regression R^2 values for the various subgroups were (1) behavior/severity, 0.956; (2) affective meaning, 0.960; (3) sensory, 0.950; and (4) cognitive/mood, 0.980. Regression analysis of the overall fatigue yielded $R^2 = 0.960$. This finding indicated that a high level of confidence and reproducibility existed in the downward trends in all fatigue data. The combination LRT supplement was safe, and no safety issues came up during the trial.¹¹⁹ Examination of scores from individuals with chronic fatigue syndrome, Lyme disease, or other diagnosis categories did not reveal major differences in overall fatigue or its reduction by the combination supplement.^{119,120}

Summary

Oral natural supplements containing membrane phospholipids, CoQ₁₀, microencapsulated NADH, L-carnitine, α -lipoic acid, and other nutrients can help restore mitochondrial function and reduce intractable fatigue in patients with chronic illnesses. The combination of these supplements can result in a safe and effective method to reduce fatigue and help restore quality of life.

Author Disclosure Statement

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