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Public Health Alert

Mitochondrial Dysfunction and Disease: Loss of Mitochondrial Function in Chronic Diseases and its Reversal with Lipid Replacement Therapy

by Prof. Garth L. Nicolson, Ph.D.*

Department of Molecular Pathology, The Institute for Molecular Medicine, Huntington Beach, CA 92647

Email: gnicolson@immed.org

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Abstract

Loss of function in mitochondria, the key cell organelle responsible for cellular energy production, can result in cell death, excess fatigue and other symptoms that are common problems in almost every chronic disease. These include: neurodegenerative diseases, diabetes and metabolic syndrome, cardiovascular diseases, autoimmune diseases, neurobehavioral and psychiatric diseases, musculoskeletal and gastrointestinal diseases, fatiguing illnesses, cancer and chronic infections, among others. At the molecular level reduction in mitochondrial function occurs when there is loss of mitochondrial maintenance, resulting in reduced efficiency of the electron transport chain. Lipid Replacement Therapy using an all-natural nutritional supplement mixture containing membrane phospholipids, mitochondrial cofactors and other ingredients can be used to repair mitochondrial damage, improve mitochondrial function and increase the efficiency of the electron transport chain. Recent clinical trials have shown the benefits of Lipid Replacement Therapy in enhancing mitochondrial function, reducing fatigue and improving mood and cognition.

Introduction

Mitochondrial dysfunction, characterized by loss of efficiency in the electron transport chain in mitochondria, the chief organelles inside cells that produce high-energy molecules such as ATP, is a characteristic of aging and essentially all chronic diseases.[1-4] The disease list includes: neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Freidriech ataxia; [1, 2, 4, 5] cardiovascular diseases, such as atherosclerosis and other heart and vascular conditions;[6, 7] diabetes and metabolic syndrome;[8-10] autoimmune diseases, such as multiple sclerosis, systemic lupus erythematosus and type 1 diabetes;[11-14] neurobehavioral and psychiatric diseases, such as autism spectrum disorders, schizophrenia,

bipolar and mood disorders;[14-16] gastrointestinal disorders;[17, 18] fatiguing illnesses, such as chronic fatigue syndrome and Gulf War illnesses;[19-21] musculoskeletal diseases, such as fibromyalgia and skeletal muscle hypertrophy/atrophy;[22, 23] cancer;[24, 25] and chronic infections.[26, 27]

The ability to produce high-energy molecules like ATP in mitochondria is directly related to the ability of the electron transport chain to pump protons across the inner mitochondrial membrane, creating a transmembrane electrical proton gradient (Δp) and electrochemical gradient ($\Delta\Psi_m$) gradient. The electrochemical gradient is used to drive ADP phosphorylation to ATP.[28, 29] A byproduct of this process is the production of Reactive Oxygen Species (ROS), highly reactive free radicals that are produced as a consequence of oxidative phosphorylation and can damage mitochondrial lipids, proteins and DNA by oxidation.[30-32] However, there are mechanisms to control the excess production of ROS, and one of these is to produce a controlled leak of protons back across the inner mitochondrial membrane by inducing uncoupling proteins that allow protons to flow back across the proton gradient.[29] In the absence of controlled proton leakage, excess oxygen consumption and resulting ROS production can damage mitochondrial membrane lipids, such as the very ROS-sensitive inner mitochondrial membrane cardiolipin. Oxidative damage of inner mitochondrial membrane cardiolipin and other membrane lipids can cause increased proton and ion leakage back across the inner membrane and partial loss of the electrochemical gradient thus causing mitochondrial dysfunction, which is seen as increased ROS and reduced ATP production while still consuming oxygen.[33]

Mitochondrial Function, Fatigue and Natural Supplements

In humans mitochondrial function is related to 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. At the cellular level, fatigue is thought to be related to loss of mitochondrial function and production of ATP.[34, 35] Chronic fatigue or intractable fatigue lasting more than 6 months that is not reversed by sleep is the most common complaint of patients seeking general medical care.[36, 37] Chronic fatigue is also an important secondary condition in many clinical diagnoses, often preceding patients' primary diagnoses.[38] Chronic fatigue has been directly related to loss of mitochondrial function[39] and production of ATP.[40]

Although natural supplements have been used to reduce fatigue, few are considered effective.[41, 42] However, Lipid Replacement Therapy (LRT®) or the use of food-derived molecules for the natural replacement of damaged, mainly oxidized, membrane lipids in mitochondria and other cellular organelles has proved very effective at reducing fatigue.[25, 35, 39, 43] To some degree, antioxidant supplements can reduce ROS and prevent some mitochondrial oxidation, but antioxidants alone cannot repair the damage already done to cells, and in particular, to their mitochondrial membranes.[44, 45]

Lipid Replacement Therapy and Fatigue

LRT® plus antioxidants have been effective in the treatment of certain clinical conditions, such as chronic fatigue.[39, 41, 43, 46,] LRT® results in the actual replacement of damaged cellular phospholipids with undamaged (unoxidized) lipids to ensure proper function of cellular membranes. Combined with antioxidants, LRT® prevents oxidative damage to cellular structures and functions and is useful in the treatment of various clinical conditions.[25, 35, 39, 41, 43] LRT® can repair mitochondrial membranes, increase mitochondrial function, and decrease fatigue in chronic fatigue syndrome, fibromyalgia syndrome, and other conditions, including aging (Table 1). When mitochondrial function was followed in parallel with fatigue in a crossover clinical trial, there was a close correspondence between loss of fatigue and gains in mitochondrial function.[39]

Lipid Replacement Therapy with Membrane Phospholipids, CoQ10, and NADH

A new LRT® formulation of membrane phospholipids (polyunsaturated phosphatidylcholine, phosphatidylglycerol, phosphatidylserine, phosphatidylinositol, and other membrane phospholipids), CoQ10 plus microencapsulated NADH and other nutrients has been developed.[48] This formulation suppressed intractable fatigue in patients with a variety of diagnoses during a two-month trial.[48] The 58 participants in this study had moderate to severe intractable fatigue for an average >17 years and had been to an average of >15 practitioners without resolution of their fatigue. These subjects included 30 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 cancer; and 2 diabetes.

Table 1. Dietary LRT® ® Supplementation Reduces Fatigue Scores in Chronically Ill Patients[a]

Subjects/patients	n	Av. age	Time on LRT® ®	Piper Fatigue Scale (PFS) fatigue reduction (%)	Reference
Chronic fatigue	34	50.3	8 wks	40.5**	Ellithorpe et al.[46]
Aging, chronic fatigue	20	68.9	12 wks	35.5*	Agadjanyan et al.[39]
Chronic fatigue syndrome (and/or fibromyalgia	15	44.8	8 wks	43.1*	Nicolson & Ellithorpe[43]
Aging, fatigue	67	57.3	1 wk	36.8*	Nicolson et al.[47]
Chronic illnesses	58	55.0	8 wks	30.7*	Nicolson et al.[48]

[a]Modified from Nicolson and Settineri[35]

**p < 0.0001, *p < 0.001 compared to without LRT® ®

These patients had tried unsuccessfully many drugs and supplements (average >35) to reduce their fatigue.[48]

Participants in the trial of chronic illness patients took the combination supplement ATP Fuel® (membrane phospholipids, CoQ10, NADH and other ingredients) for 8 weeks, and fatigue was scored using the Piper Fatigue Scale (PFS).[38] The PFS is a validated instrument that measures four dimensions of subjective fatigue: behavioral/severity, affective/ meaning, sensory, and cognitive/mood.[38] These were used to calculate the four subscale/dimensional scores and the total fatigue scores.[48]

In this study on 58 long-term chronic illness patients with intractable fatigue the initial PFS mean total fatigue score ± SD was 7.51 ± 0.29, and after 8 weeks of supplement this improved to 5.21 ± 0.28, or a 30.7% reduction in fatigue. The mean decrease in fatigue scores was significant by t-test ($p < 0.0001$) and Wilcoxon signed-rank ($p < 0.0001$) analyses.[48] The PFS fatigue scores can be further dissected into four subcategories (Behavior/Severity subcategory, which deals with completing tasks, socializing, engaging in sexual activity and other activities, and intensity or degree of fatigue; Affective/Meaning subcategory, which determines fatigue/tiredness is pleasant/unpleasant, whether the patient is agreeable/disagreeable, protective/destructive, or feels normal/abnormal; Sensory subcategory, which determines whether the patient is strong/weak, awake/sleepy, refreshed/tired, or energetic/unenergetic; and Cognitive/Mood subcategory, which assesses whether a patient feels relaxed/tense, exhilarated/depressed, able/unable to concentrate, remember, and think clearly). All of these subcategories showed significant reductions by the end of the 8-week trial ($p < 0.0001$), indicating that there were significant improvements in all subcategories of fatigue. For example, there was a 30.7% reduction ($p < 0.0001$) in severity/behavior of fatigue, indicating that there was 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, there was a 28.0% improvement ($p < 0.0001$) in mood and cognitive ability, such as the ability to concentrate, remember, and think clearly.[48]

Regression Analysis of Fatigue Data

To determine if the trends in fatigue reduction over time during the trial on the combination supplement (membrane phospholipids, CoQ10, NADH and other ingredients) were consistent, occurred with a high degree of confidence, and could predict further reductions in fatigue, we conducted regression analyses of the data.[48] The regression analysis of overall fatigue and in 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 R2 values for the various subgroups were: behavior/severity, 0.956; affective meaning, 0.960; sensory, 0.950; and cognitive/mood, 0.980. Regression analysis of the overall fatigue yielded a R2 = 0.960. This indicated that there was a high level of confidence and reproducibility in the downward trends in all fatigue data. The combination supplement ATP Fuel® was also safe, and there were no safety issues that came up during the trial.[48]

In previous trials using LRT® the most severely fatigued subjects showed the greatest reductions in fatigue scores.[39, 46] For example, subjects with initial overall fatigue scores indicating severe fatigue (above 8 in the PFS scale) showed greater reductions in fatigue scores on day 60 (35.3% improvement in overall fatigue) than subjects with lower scores (moderate fatigue, initial PFS score 4–8, 25% improvement). Examination of scores from patients 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.[48]

Effects of CoQ10 and NADH Without LRT® ®

Some but not all previous clinical studies on CoQ10 or NADH reported some positive effects on fatigue. However, in these studies only a subset of patients responded or the response was for a limited time.[49, 50] In a study on chronic fatigue syndrome patients 8 of 26 (30.7%) responded to microencapsulated NADH compared with 2 of 26 (8%) on placebo ($p < 0.05$).[49] These results were not considered significant by others.[50] The use of oral NADH compared to psychological/nutritional therapy for 31 chronic fatigue syndrome patients revealed that NADH alone reduced fatigue in the first 4 months of a 12 month trial.[51] After the first 4 months, symptom scores were similar in the NADH and psychological/nutritional arms of the trial. Oral NADH given for two months to chronic fatigue syndrome patients resulted in a decrease in anxiety and maximum heart rate after a stress test, but little or no difference was found in the functional impact of fatigue, quality of life, sleep quality, exercise capacity, or functional reserve.[52]

Cofactor CoQ10 is an important antioxidant and an essential component in the mitochondrial respiratory chain as well as a molecule involved in gene regulation.[53] CoQ10 has been used as a dietary supplement in a variety of chronic illnesses and age-related conditions.[53, 54] In the combination supplement used by us (ATP Fuel®) CoQ10 was used to improve energy transduction and combat oxidative stress.[54]

Summary

We used a combination oral supplement containing a mixture of membrane phospholipids, CoQ10, and microencapsulated NADH to significantly reduce intractable fatigue in patients with chronic fatigue syndrome, fibromyalgia syndrome, Gulf War illness, chronic Lyme disease, and other conditions. These patients had been symptomatic for an average of over 17 years, had been seen by multiple practitioners (>15), and had used many other supplements and drugs (>35) without apparent reductions in their fatigue. The combination supplement was a safe and effective method to significantly reduce fatigue in patients with intractable chronic fatigue.[48]

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