Mitochondrial Dysfunction and Chronic Disease: Treatment with Membrane Lipid Replacement and Other Natural Supplements

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Abstract Mitochondria provide most of our cellular energy needs; therefore, mitochondrial dysfunction can cause fatigue and other symptoms that are commonly found in every chronic and many acute conditions. Reductions in mitochondrial function occur when there is loss of maintenance of inner mitochondrial membrane trans-membrane potential, modifications in the electron transport chain, damage to mitochondrial DNA, altered mitochondrial transcription, and reductions in the transport of critical substrates and metabolites into mitochondria. These events can result in reduced efficiency of oxidative phosphorylation and reductions in ATP production. Several components of mitochondria require routine replacement, and this can be facilitated with dietary changes and the use of natural supplements. Clinical trials have shown the utility of using oral mitochondrial replacement supplements, such as replacement glycerolphospholipids, L-carnitine, alpha-Lipoic acid, coenzyme Q10, NADH, pyrroloquinoline quinone and other mitochondrial supplements to improve mitochondrial function. Membrane Lipid Replacement supplements with or without other mitochondrial supplements can significantly

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diminish fatigue and other mitochondria-associated symptoms found in aging, cancer and chronic diseases.

Keywords Membranes · Phospholipids · Coenzyme Q10 · L-Carnitine · Alpha-Lipoic acid · Fatigue · Mitochondrial function · Metabolite transport · Chronic diseases · Cancer · Aging

1 Introduction

Mitochondria are thought to perform multiple functions beyond their energy production, including the regulation of cellular communication, nuclear gene expression, synaptic transmission, inflammatory responses, and complex metabolic pathways (Picard et al. 2016). Mitochondria are absolutely required for health, and if mitochondria become dysfunctional, a number of adverse events ensue that result in illness (Piecznik and Neustadt 2007). Mitochondrial dysfunction is most often characterized by loss of efficiency in the electron transport chain (ETC) and resulting decreased synthesis of high-energy molecules, such as ATP (Aw and Jones 1989; Smeitink et al. 2006). The dysfunctinal state of mitochondria is so comonly found that it is a characteristic of aging and essentially all chronic and some acute diseases (Green et al. 2011; Nicolson 2014; Nicolson and Ash 2014, 2017; Picard et al. 2016; Piecznik and Neustadt 2007; Reddy 2008; Reddy and Reddy 2011; Smeitink et al. 2006).

In terms of chronic, non-genetic diseases, the most obvious illnesses that are typified by mitochondrial dysfunction are the fatiguing illnesses, such as chronic fatigue, chronic fatigue syndrome, myalgic encephalomyelitis, fibromyalgia and Gulf War illness (Agadjanyan et al. 2003; Booth et al. 2012; Breeding et al. 2012; Cordero et al. 2010; DiMauro and Rustin 2009; Myhill et al. 2009; Morris and Maes 2014; Nicolson 2014; Nicolson and Nicolson 1996; Nicolson et al. 2003; Norheim et al. 2011; Park et al. 2000). In addition to the fatiguing illnesses, this list also includes: (1) cardiovascular diseases, such as atherosclerosis and other heart and vascular conditions (Limongelli et al. 2012; Nicolson 2007; Rabinovich and Vilaro 2010; Victor et al. 2009); (2) metabolic diseases, such as metabolic syndrome and type 2 diabetes (Joseph et al. 2012; Ma et al. 2012; Nicolson 2007); (3) neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and Freidriech ataxia (Ghafourifar et al. 2008; Karbowski and Neutzner 2012; Mao and Reddy 2010; Reddy 2008; Reddy and Reddy 2011); (4) autoimmune diseases, such as systemic lupus erythematosus, multiple sclerosis and type 1 diabetes (Fernandez and Perl 2009; Fernandez and Perl 2009; Maiese et al. 2007; Mao and Reddy 2010); (5) neurobehavioral and psychiatric diseases, such as schizophrenia, bipolar and mood disorders and autism spectrum disorders (Konradi et al. 2004; Marazziti et al. 2012; Palmieri and Peerscio 2010; Prince et al. 2000; Rossignol and Frye 2012; Stork and

Table 1 Some natural ingredients and cofactors that have been used or suggested to treat mitochondrial dysfunction[a]

Category	Some examples
Minerals	Magnesium, calcium, phosphate
Vitamins	Vitamins C, D and E, thiamine, riboflavin
Metabolites	Creatine, pyruvate
Cofactors	CoQ10, NADH, alpha-lipoic acid, nicotinic acid
Lipids	Membrane glycerolphospholipids, unsaturated fatty acids
Transporters	L-Carnitine, membrane phospholipids
Antioxidants	CoQ10, alpha-lipoic acid, NADH, glutathione, resveratrol
Enzyme inhibitors	Alpha-lipoic acid, dichloroacetate
Biogenesis stimulants	Pyrroloquinoline quinone
Herbs	Curcimin, schisandrin

[a]Modified from Kerr (2010) and Nicolson (2014)

Renshaw 2005); (6) gastrointestinal disorders (Breeding et al. 2012; Chitkara et al. 2003; Di Donato 2009); (7) chronic infections (Anand and Tikoo 2013; Ashida et al. 2011); (8) cancers (Gabridge 1987; Nicolson 2010; Sotgia et al. 2011; Wallace 2005); and (9) sytemic environmantal contaminantion (Leung et al. 2013; Mayer et al. 2013).

Genetic alterations in mitochondrial genes also contribute to mitochondrial dysfunction. This has been reviewed elsewhere (Kerr 2010; Holt 2010; Picard et al. 2016; Wallace and Fan 2010) and will not be part of this review. Here we will concentrate on non-genetic or acquired mechanisms that could explain mitochondrial dysfuction and its treatment with natural supplements. We will also discuss the use of Membrane Lipid Replacement (MLR) strategies using glycerolphospholipid supplements (Nicolson 2010, 2014, 2016; Nicolson and Ellithorpe 2006; Nicolson and Ash 2014, 2017; Nicolson et al. 2016) and combinations of natural supplements that include antioxidants, vitamins, minerals, enzyme cofactors, metabolites, transporters, and other natural products (Table 1) (Nicolson 2014; Nicolson et al. 2012a, b).

2 Mitochondrial Membrane Dysfunction

There are several reasons for mitochondria failing to provide enough necessary high energy molecules for cell and tissue functions. For example, there could be an inadequate number of mitochondria, damaged mitochondrial membranes, a problem in providing the necessary substrates for mitochondrial function, mitochondial genetic damage or defects in the ETC or ATP synthesis machinery of the mitochondrial inner membrane (MIM) (Nicolson 2014; Nicolson and Ash 2014, 2017).

Inside cells the numbers, locations and functional status of mitochondria can be changed by several processes, such as the fusion of partially dysfunctional mitochondria in order to provide enough undamaged components to improve overall function, the generation of entirely new mitochondria from existing mitochondria by fission, and the removal and degradation of dysfunctional mitochondria in a process called mitophagy (Mishra and Chan 2016; Twig and Shirihi 2011). Mitophagy and the fission and fusion of mitochondria are controlled by complex cellular processes that sense the deterioration of mitochondria. For example, some of mitochondrial properties that characterize deterioration of mitochondria are the depolarization of the MIM and the activation of certain transcription pathways (Lee et al. 2012; Priault et al. 2005).

The MIM is especially sensitive to environmental and cellular changes, and the ability of the MIM to produce high-energy molecules like ATP is directly related to the capacity of the ETC to convert the energy of metabolites to NADH and transfer electrons from the ETC to molecular oxygen while simultaneously pumping protons from the mitochondrial matrix across the MIM to the intermembrane space. This process creates trans-membrane proton (Δp) and electrochemical gradients ($\Delta\Psi_m$) across the MIM that are critical for mitochondrial function (Nicholls 2010; Rich and Marechal 2010). The trans-membrane potential created by the proton gradient can then use ATP synthase to flow protons back across the MIM, using the energy from this process to synthesize ATP (Divakaruni and Brand 2011; Nicholls 2010). Since MIM trans-membrane potential is directly related to ETC function through reversible phosphorylation, mitochondrial dysfunction can be monitored by the loss of MIM trans-membrane potential. In higher organisms, the normal MIM trans-membrane potential associated with an efficient energy production is approximately −120 mV (Hüttemann et al. 2008).

An interesting and important consequence of the transfer of electrons through the ETC is the production of Reactive Oxygen Species (ROS), highly reactive free radicals that are produced as a byproduct of oxidative phosphorylation. Although these oxidant molecules can be produced by other events inside cells, significant sources of ROS and related Reactive Nitrogen Species (RNS) are the mitochondria. Low concentrations of ROS are essential as secondary cellular messengers, for example, passing messages between the mitochondria and the nucleus (Reczek and Chandel 2015). However, high concentrations of ROS and RNS can react with and damage cellular DNA, lipids and proteins (Richter et al. 1998; Spiteller 2010; Spector and Yorek 1985; Stadtman 2002).

The appropriate balance of ROS and RNS concentrations within cells is essential in order to maintain cellular homeostasis—thus there are natural mechanisms inside cells to neutralize excess ROS/RNS. Among the mechanisms that control ROS/RNS concentrations, the most important are dismutase enzymes and antioxidants that are used to neutralize exces amounts of ROS/RNS (Duchen and Szabadkai 2010; Nicholls 2010). In addition to the conrolled flow of protons across the MIM that allows ATP production, the leakage of protons back across the MIM can also be facilitated by inducing uncoupling proteins that allow protons to flow back across the proton gradient (Nicholls 2010; Rich and Marechal 2010). This reduces the

production of ATP while still consuming excess oxygen (Duchen and Szabadkai 2010). This process has been described as a controlled proton leak, where excess oxygen is consumed in the process (Divakaruni and Brand 2011). The resulting excess ROS that is produced as a byproduct of this process, however, can damage mitochondrial as well as other cellular membrane lipids, proteins and DNA (Divakaruni and Brand 2011; Richter et al. 1998; Wei and Lee 2002). Since membrane phospholipids maintain membrane matrix structure and associate and stabilize critical membrane proteins, phospholipid modification by events such as peroxidation is an important cause of mitochondrial dysfunction, which in turn is linked to fatigue and aging-associated diseases (Ademowo et al. 2017).

Within the mitochondria the most sensitive substrates of ROS and RNS oxidation are the MIM lipids, especially the MIM cardiolipin. Cardiolipin is a specialized phospholipid that is highly integrated into the ETC. It is bound by essential proteins in the MIM, and is absolutely required for mitochondrial ETC function (Spector and Yorek 1985). Alterations in cardiolipid have profound consequences for the function and activity of the ETC (Chicco and Sparagna 2007; Houtkooper and Vaz 2008). Although the exact molecular mechanisms that yield peroxidized lipids, such as the cardiolipins, are still poorly understood, the formation of 4-hydroxynoneal reactive lipids seems to be a common intermediate pathway for many of the events leading to lipid peroxidation (Xiao et al. 2017). ROS and RNS damage to MIM cardiolipin and other membrane phospholipids can result in increased proton and ion leakage back across the MIM and partial loss of the proton/electrochemical gradient. Since cardiolipin provides stability for the cytochrome/enzyme complexes in the MIM, its damage by ROS/RNS results in loss of ETC function and can result in initiation of mitophagy (Houtkooper and Vaz 2008).

Cellular antioxidant defenses neutralize excess oxidants, and this usually maintains ROS/RNS levels at concentrations that prevent excess damage to cellular molecules (Barber and Harris 1994; Sun 1990). Some of the most important endogenous cellular antioxidant defenses are glutathione peroxidase, catalase and superoxide dismutase, among others (Fridovich 1995; Jagetia et al. 2003; Sun 1990). These antioxidant defense enzymes are essential in preventing excess damage to cells and initiating cell death programs.

There are also low molecular weight antioxidants that can affect ROS/RNS levels, and some of these can be provided by dietary supplementation (Aeschbach et al. 1994; Jagetia et al. 2003; Schwartz 1996). Dietary antioxidants have been used as natural preventive agents to shift the levels of oxidative molecules to physiological levels that can be maintained in redox balance by the natural cellular antioxidant system (Prasad et al. 2001). However, dietary antioxidants alone cannot provide replacement molecules for damaged cellular and mitochondrial components.

Finally, calcium levels inside mitochondria are also related to the normal function of mitochondria (Marchi et al. 2017). The balance of calcium in mitochondria is maintained through a variety of ion channels and transporters in mitochondrial membranes. For example, mitochondrial permeability transition pore (mPTP), calcium uniporter, mitochondrial BK channels, among other mitochondrial membrane components, maintain intra-mitochondria calcium levels (Pérez and Quintanilla

2017; Satrustegui et al. 2007). The function of these channels and transporters is influenced and dependent on the lipid composition of the mitochondrial membrane (Lee 2004; Szabo et al. 2004).

3 Fatigue and Mitochondrial Dysfunction

Fatigue is a multidimensional sensation that is perceived to be a lack of overall energy, an inability to perform even simple tasks without exertion, and prolonged recovery required after physical activity. Although the etiologic mechanisms that cause fatigue are not well understood, fatigue is a hallmark symptom of mitochondrial dysfunction (Filler et al. 2014). Mild fatigue can be caused by different conditions, including depression and other psychological conditions, but moderate to severe fatigue involves cellular energy systems, such as those provided by mitochondria (Kroenke et al. 1988; Nicolson 2010; Nicolson and Settineri 2011). At the tissue and cellular level moderate to severe fatigue is related to loss of mitochondrial ETC function and reduced production of ATP (Booth et al. 2012; Myhill et al. 2009; Nicolson 2007, 2010; Nicolson and Ash 2014, 2017).

There are different types of fatigue, including short-term fatigue, often associated with physical exertion, and long-lasting or chronic fatigue. Intractable fatigue lasting more than 6 months that is not reversed by sleep is generally considered to be chronic fatigue, and this is the most common complaint of patients seeking general medical care (Kroenke et al. 1988; Morrison 1980). Fatigue and chronic fatigue are important secondary symptoms in many clinical conditions, and they often occur early in the progression of disease (Kroenke et al. 1988).

Mitochondrial dysfunction is directly related to excess fatigue that is not reversed by rest. During aging and chronic diseases oxidative ROS/RNS damage to mitochondrial membranes and the ETC decreases mitochondrial function, which is perceived as fatigue (Huang and Manton 2004; Logan and Wong 2001), and when this persists for some time it is perceived as chronic fatigue. Chronic fatigue often presents with additional symptoms, among them musculoskeletal pain, sleep disturbance, cognition and memory problems, headaches, digestive symptoms and other complaints. These chronic fatigue-associated symptoms have been collectively described as chronic fatigue syndrome (CFS) (Fukuda et al. 1994). CFS pateints also show evidence of oxidative damage, such as oxidative damage to DNA and lipids (Logan and Wong 2001; Manuel y Keenoy et al. 2001), oxidized blood markers (Richards et al. 2000) and oxidatively damaged membrane lipids, including sphingolipids and glycosphingolipids (Fulle et al. 2000). CFS patients also have continuously elevated levels of peroxynitrite due to excess nitric oxide. RNS such as peroxynitrite can cause lipid peroxidation and loss of mitochondrial function as well as changes in cytokine levels that exert a positive feedback on nitric oxide production (Pall 2000).

4 Membrane Lipid Replacement and Mitochondrial Dysfunction

The dietary replacement of cellular membrane glycerolphospholipids using natural whole foods is a difficult way to provide enough lipid replacement molecules on a daily basis (Nicolson and Ash 2014, 2017). To more efficiently remove and replace damaged, oxidized, membrane phospholipids in mitochondria and other cellular organelles specific dietary supplements have been used. For example, Membrane Lipid Replacement (MLR) with antioxidants has proved very effective in replacing damaged, oxidized cellular lipids and restoring function to organelles such as mitochondria (recently reviewed in Nicolson 2016; Nicolson et al. 2016; Nicolson and Ash 2014, 2017). To various degrees antioxidant supplements can reduce ROS/RNS levels and prevent some membrane phospholipid oxidation (Prasad et al. 2001; Schwartz 1996), but antioxidants alone cannot repair the damage done to cellular membranes, and in particular, to their mitochondria ETC and other critical membrane systems (Nicolson and Ash 2014, 2017).

The MLR use of oral membrane glycerolphospholipids with unsaturated fatty acids in doses ranging from 2–4 g per day along with antioxidants has proven safe and effective for the natural medicine treatment of certain conditions, such as fatiguing illnesses (reviewed in Nicolson 2016; Nicolson and Ash 2014, 2017; Nicolson et al. 2016). MLR results in the actual replacement of damaged membrane phospholipids with undamaged (unoxidized) phospholipids with unsaturated fatty acids to ensure proper functioning of cellular and intraellular membranes. The reason that MLR has been so effective is likely due to the natural process of lipid uptake and transport, which can translocate and transport high concentrations of dietary phospholipids as lipid granules, liposomes, droplets, vesciles and lipoproteins in a ‘bulk flow’ gradient process that disseminates the MLR lipids to every cell and tissue and returns damaged, oxidized phospholipids for excretion by the same ‘bulk flow’ process (Nicolson and Ash 2017).

In clinical situations, oral MLR phospholipids can increase mitochondrial ETC function and decrease fatigue in CFS, fibromyalgia, and other fatiguing conditions, including natural aging (Table 2). For example, a membrane phospholipid-vitamin mixture (Propax™ with NTFactor®) was utilized by Ellithorpe et al. (2003) in a study on aging patients with severe chronic fatigue and was found to reduce fatigue by 40.5% within 8 weeks. Also, a cross-over study was initiated to study the effects of MLR phospholipids on fatigue and mitochondrial function in patients with moderate to severe chronic fatigue (Agadjanyan et al. 2003). Oral administration of NTFactor® for 12 weeks resulted in a 35.5% reduction in fatigue and 26.8% increase in mitochondrial function. Switching these patients to placebo without their knowledge resulted in slow increases in fatigue along with decreases in mitochondrial function towards control levels. Similar levels of fatigue reduction were observed in CFS and fibromyalgia patients given oral MLR phospholipids for 8 weeks (Nicolson and Ellithorpe 2006). The timing of fatigue reduction may depend on the oral MLR supplement used and whether it is combined with other supplements. For example,

Table 2 Some examples of oral membrane glycerolphospholipid supplementation and effects on fatigue in chronic illnesses[a]

Subjects/patients	n	Av. age	Time on MLR	Fatigue Scale fatigue reduction (%)	References
Chronic fatigue	34	50.3	8 weeks	40.5**	Ellithorpe et al. (2003)
Aging, chronic fatigue	20	68.9	12 weeks	35.5*	Agadjanyan et al. (2003)
Chronic fatigue syndrome (and/or fibromyalgia syndrome)	15	44.8	8 weeks	43.1*	Nicolson and Ellithorpe (2006)
Aging, fatigue	67	57.3	1 week	36.8*	Nicolson et al. (2010)
Chronic illnesses	58	55.0	8 weeks	30.7*	Nicolson et al. (2012a)
Chronic fatigue syndrome	30	56.2	8 weeks	34.3*	Nicolson et al. (2012a)
Lyme disease	18	52.4	8 weeks	26.7*	Nicolson et al. (2012b)
Gulf War illnesses	16	42.2	8 weeks	34.6*	Nicolson et al. (2012a)

**$p < 0.0001$, *$p < 0.001$ compared to no supplement
[a]Modified from Nicolson (2016)

using a higher dose formulation of NTFactor® and adding vitamins, minerals and other supplements in patients with moderate chronic fatigue resulted in a 36.8% reduction in fatigue within 1 week (Nicolson et al. 2010).

In multiple studies in animals and humans the use of MLR supplements has proven to be incredibly safe, and there was absolutely no evidence of any type of toxicity or adverse events (reviewed in Nicolson and Ash 2014, 2017). Up to 45 g of MLR phospholipids have been administered per day without any evidence of toxic effects (Polinsky et al. 1980). In fact, high doses of MLR phospholipids have had the opposite effect—they actually reduced the adverse symptoms caused by drugs and other treatments (reviewed in Nicolson 2010; Nicolson and Ash 2017).

5 Other Natural Supplements and Mitochondrial Dysfunction

A number of natural dietary supplements have been used to reduce non-psychological fatigue and increase mitochondrial function (DiMauro and Rustin 2009; Nicolson 2014; Nicolson and Settineri 2011). Some of these supplements include vitamins, minerals, antioxidants, metabolites, enzyme inhibitors and cofactors, mitochondrial transporters, herbs and membrane phospholipids (Table 1). As interventions for the treatment and management of patients' symptoms, such as fatigue, several dietary

supplements have been utilized. However, for the most part they have not been considered effective (Chambers et al. 2006). Some of the most promising supplements beyond MLR are listed in Table 1 and discussed below.

5.1 Coenzyme Q10

The mitochondrial cofactor coenzyme Q10 (CoQ10) or ubiquinone is a key component of the mitochondrial ETC and one of the most widely used natural supplements that target mitochondrial dysfunction (Mancuso et al. 2010; Orsucci et al. 2011; Potgieter et al. 2013; Rich and Marechal 2010). CoQ10 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 (Groneberg et al. 2005; Littarru and Tiano 2010). The main use of CoQ10 as a natural supplement has been to improve the efficiency of electron transfer between the various complexes of the ETC (Littarru and Tiano 2010; Mancuso et al. 2010).

An important use of CoQ10 suppelments has been to increase the levels of cellular CoQ10 in various conditions that typically show reduced CoQ10 levels (Mancuso et al. 2010; Orsucci et al. 2011). For example, analysis of patient samples shows reduced levels of CoQ10 in neuromuscular and neurodegenerative diseases, such as Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, Friedreich's ataxia and other disorders (Mancuso et al. 2009, 2010).

CoQ10 supplements have been used to reduce symptoms and progression in neurodegenerative diseases (Littarru and Tiano 2010; Mancuso et al. 2009; Yang et al. 2010). In a randomized, placebo-controlled clinical trial on 98 Alzheimer's patients Galasko et al. (2012) used a mixture of CoQ10, vitamins C and E and alpha-Lipoic acid in the test arm. When the trial was completed, patients in the test arm showed significant reductions in oxidative stress markers compared to placebo, but did not show significant changes in cerebrospinal fluid markers related to beta-amyloid or tau pathology. Parkinson disease patients generally showed increased oxidized-to-total CoQ10 ratios as well as significant increases in markers of oxidative damage in the cerebrospinal fluid (Isobe et al. 2010). This situation can be partially reversed with CoQ10 administration. In patients with early Huntington's disease CoQ10 administration for 30 months slowed the usual decline in total functional capacity but the differences were not statistically significance (Kieburtz and Huntington Study Group 2001).

Many of the neurodegenerative disease studies with CoQ10 supplementation did not reach clinical significance. For example, a randomized, placebo-controlled, multi-center phase II trial with amyotrophic lateral sclerosis patients given CoQ10 did not show differences in functional decline over a 9 month period (Thompson et al. 2009).

Other uses of CoQ10 supplementation include physical performance, hypertnesion and coronary heart disease. Mortensen et al. (2014) and Rosenfeldt et al. (2003) have reviewed the use of CoQ10 supplements for improving physical exercise,

hypertension and heart failure. In 6 of 11 of the published studies modest improvements in exercise capacity were found in the subjects given dietary CoQ10. In eight publications on the effects of CoQ10 on hypertension there was a mean decrease in systolic blood pressure (16 mmHg) and diastolic pressure (10 mmHg). In nine randomized trials on the use of CoQ10 in heart failure patients there were non-significant trends towards increased injection fraction and reduced mortality. For example, Rosenfeldt et al. (2003) utilized a randomized, placebo-controlled trial to study the effects of oral CoQ10 in 35 patients with heart failure. They found in the test arm, but not in the control arm, that patients had significant improvements in symptoms and a trend towards improvements in mean exercise times. In a randomized, placebo-controlled, multi-center trial on chronic heart failure Mortensen et al. (2014) found that although there were no significant differences in short-term endpoints, the long-term use of CoQ10 resulted in lower cardiovascular mortality (9% versus 16%), all-cause mortality (10% versus 18%) and hosptial stays in the test arm of the study.

The effects of administration of oral CoQ10 during physical exercise have also been examined in a placebo-controlled, blinded, cross-over trial. Healthy subjects received CoQ10 or placebo for 8 days, and their performance was then evaluated at fixed workloads on a bicycle ergometer with a rest period in-between (Mizuno et al. 2008). While on CoQ10 the subjects were able to achieve higher work outputs. They also had less fatigue, and their need for more recovery time was reduced compared to the placebo arm.

To improve the delivery of CoQ10 to mitochondria hydrophobic carriers have been used. For example, the products MitoQ and SkQ are derivatives of quinone covalently conjugated to lipophilic cations to imrove the delivery of CoQ10 to mitochondria. By using hydrophobic derivatives of CoQ10 to increase the transfer of CoQ10 to mitochondrial MIM cardiolipin peroxidation by ROS could be largely prevented (Feniouk and Skulachev 2017).

5.2 Alpha-Lipoic Acid

Alpha-Lipoic acid (1,2-dithiolane-3-pentanoic acid) is an anti-inflammatory agent, potent antioxidant, transition metal ion chelator and redox transcription regulator (Marczurek et al. 2008; Shay et al. 2009; Smith et al. 2004). Alpha-Lipoic acid is also an important cofactor in mitochondrial alpha-ketoacid dehydrogenases, and thus it is a critical cofactor in mitochondrial oxidative decarboxylation reactions (Shay et al. 2009). In terms of its clinical use alpha-Lipoic acid has been utilized as an oral supplement in the treatment of complications associated with diabetes mellitus, where it has been shown to reduce various diabetic-associated neuropathies, inflammation and vascular health (Chambers et al. 2006; Marczurek et al. 2008). Glucose uptake and metabolism are also affected by alpha-Lipoic acid (Estrada et al. 1997).

In chronic illnesses and during natural aging certain sphingolipids, especially ceramides, and in particular short-chain ceramides, accumulate in mitochondria. This occurs due to hydrolysis of sphingomyelin by sphingomyelinase. If accumulation occurs over a certain threshold, eventually the excess ceramides can reduce ETC activity (Di Paola et al. 2000; Gudz et al. 1997). Ceramide accumulation in mitochondria is especially damaging to mitochondria in cardiac tissue. Thus feeding aging rodents with dietary alpha-Lipoic acid has been used to lower ceramide levels in vascular endothelial cells of cardiac muscle, and this has resulted in a restoration of mitochondrial glutathione levels—the result was increased ETC function (Monette et al. 2011).

There are certain uses of alpha-Lipoic acid that have proven to be effective. For example, in diabetes patients alpha-Lipoic acid has been used to reduce diabetic complications, such as sensorimotor polyneuropathies (Ziegler et al. 2004). In a 4-year blinded study that used oral alpha-Lipoic acid supplementation in diabetic patients neuropathic impairments improved significantly but not attributes of nerve conduction. Alpha-Lipoic acid was found to be safe for long-term use in diabetic patients (Ziegler et al. 2004).

When given as an oral supplement, alpha-Lipoic acid rarely accumulates in tissues above micromolar levels. Because of this, Shay et al. (2009) have argued that alpha-Lipoic acid is unlikely to be directly involved as an important primary cellular antioxidant. On the other hand, alpha-Lipoic acid can increase cellular glutathione levels by regulating glutathione synthesis and thus reducing cellular oxidative stress (Yoshida et al. 1995). In addition, alpha-Lipoic acid can have effects on the regulation of the nuclear transcription factor NF-κB. Because of its effects on transcription factor NF-κB, alpha-Lipoic acid may cause widespread transcriptional effects (Goraca et al. 2011). Alpha-Lipoic acid also has transition metal chelation properties and can remove excess copper, iron and other metals from cells. These metal can accumulate in chronic diseases, such as hemochromatosis, end-stage renal failure, Alzheimer's and Parkinson's diseases, and thus alpha-Lipoic acid has been promoted as a potential therapeutic agent in heavy metal poisoning (Smith et al. 2004). Finally there are reports that alpha-Lipoic acid also improves cognitive function along with its positive effects on mitochondrial function, suggesting a link between oxidative damage to mitochondria and congnition (Head et al. 2009).

Alpha-Lipoic acid supplementation has been promoted as a useful supplement for fatigue, although it has not been used as a sole supplement in clinical trials on chronic fatigue and CFS (Shay et al. 2009). However, due to its widespread use as a safe oral supplement (usually at 200–600 mg/day) alpha-Lipoic acid has been added to many mitochondrial support supplement mixtures to support mitochondrial function and reduce oxidative stress (Goraca et al. 2011; Nicolson et al. 2012a, b; Ziegler et al. 2011).

5.3 L-Carnitine

L-Carnitine (3-hydroxy-4-*N*-trimethylaminobutyrate), a naturally occurring fatty acid transporter, is directly involved in the transport of fatty acids into the mitochondrial matrix and in the removal of excess acyl groups. L-Carnitine functions in beta-oxidation and is important in the regulation of coenzyme A homeostatasis (Marcovina et al. 2012; Reuter and Evans 2012). Due to its mode of action L-carnitine must be maintained within a relatively narrow concentration range. Thus dietary supplementation of L-carnitine is important in maintaining its concentration within cells (Reuter and Evans 2012). When L-carnitine falls below essential concentrations, mitochondrial function deteriorates. For example, L-carnitine deficiency disorders are associated with reduced mitochondrial function, and this is further associated with insulin resistance and coronary artery disease (Koves et al. 2008; Newgard et al. 2009; Shah et al. 2009).

It has been known for some time that physicial performance is dependent on the use of L-carnitine. Supplements containing L-carnitine have been extensively by athlethes to improve performance (Spriet et al. 2008). The rationale has been that increasing the reliance on fat as the principle substrate for energy production during extreme exercise reduces the need for carbohydrates and delays the depletion of carbohydrate stores. The use of fat instead of sugars can increase overall energy production and reduce exercise-induced fatigue. L-Carnitine plays an important role in increasing the transport of fatty acids into mitochondria for their use as substrates. However, supplementation with oral L-carnitine for several weeks prior to extreme exercise did not increase skeletal muscle carnitine content, and thus during extreme exercise it is unlikely that L-carnitine supplementation alters muscle metabolism (Brass 2000; Wachter et al. 2002).

Oral L-carnitine has been used in clinical disorders that are characterized by low L-carnitine concentrations or impaired fatty acid oxidation, such as diabetes, sepsis, renal disease and cardiomyopathy (Yoshida et al. 1995). In patients with congestive heart failure L-carnitine supplementation has been used to improve physicial status. For example, in a small study of 18 patients with congestive heart failure compared to 12 placebo controls propionyl-L-carnitine supplementation improved peak heart rate (12%), exercise capacity (21%) and peak oxygen consumption (45%) in the treatment group (Anand et al. 1998). Other uses for L-carnitine supplementation include alcoholism, hepatic encephalopathy, coronary heart diseases, Peyronie's disease, cerebral ischemia and infertility (Anon 2010).

L-Carnitine has also been used as an anti-aging suppement. It is known that the rate of mitochondrial oxidative phosphorylation naturally declines during aging. In animals acetyl-L-carnitine was found to reverse age-related decreases in L-carnitine levels and increase fatty acid metabolism. L-Carnitine supplementation also reversed age-related declines in cellular glutathione levels while improving mitochondrial complex IV activity (Brass 2000). Although L-carnitine dietary supplementation at doses up to 2 g per day has been reported to be safe and potentially useful in increasing mitochondrial function in the aged, multiple clinical trials that show its

effectiveness in age-related chronic illnesses are lacking (Anon 2010). An exception to this was a randomized, controlled clinical trial using 70 centenarians who were treated with L-carnitine for 6 months. Before the trial participants were found to have muscle weakness, decreasing mental health, impaired mobility and poor endurance. By the end of the trial the treated group showed significant improvements in physical fatigue, mental fatigue and fatigue severity. The participants also showed reductions in total fat mass, increased muscle mass and increased physical and cognitive activity (Malaguarnera et al. 2007).

5.4 Reduced Nicotinamide Adenine Dinucleotide (NADH)

NADH is a cellular redox cofactor in over 200 redox reactions, and it is also a substrate for many enzymes (Penberthy 2009; Kirkland 2009). NAD/NADH also performs a balancing act between the nucleus and mitochondria over the control of cellular energy homeostasis (Canto et al. 2015). There is a universal requirement for NAD/NADH, and its deficiency results in pellagra, which is characterized by dermatitis, diarrhea, dementia and eventually death (Penberthy 2009). In the mitochondria NADH delivers electrons from metabolite hydrolysis to the ETC, but in its reduced form NADH can also act as a strong antioxidant. The usual dietary supplementation has been the use of 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 in the gastrointestinal system. This turns out to be more effective than using large oral doses of NADH, which are susceptible to oxidation and degradation and are generally considered ineffective (Kirkland 2009).

In many diseases, such as neurodegenerative diseases, oxidative damage is extensive, and various mitochondrial antioxidants have been used to treat disease and delay progression (Aw and Jones 1989; Kerr 2010; Piecznik and Neustadt 2007; Reddy 2008; Smeitink et al. 2006). Use of oral NADH in unstabilized or stablized form has resulted in mixed results. In Alzheimer's disease Birkmayer (1996) used stabilized oral NADH to improve cognitive functioning and dementia. However, in another clinical trial there were no improvements in cognition or dementia using oral NADH (Rainer et al. 2000). In a controlled trial using 26 Alzheimer's patients who were supplemented with stabilized NADH or placebo Demarin et al. (2004) found significantly better performance scores in the test arm compared to the placebo arm in verbal fluency and visual construction, with a trend toward increased performance on abstract verbal reasoning. In this trial there was no evidence of better performance in attention, memory or on scores of dementia severity (Demarin et al. 2004).

In order to bypass the problems with oral NADH supplementation Birkmayer et al. (1993) use stabilized oral NADH and IV NADH to reduce the symptoms of Parkinson's disease. In an open label trial using over 800 Parkinson disease patients the effects of IV and oral NADH was studied. Birkmayer et al. (1993) found that

19.3% of patients exhibited 30–50% improvements in disability, while 58.8% had moderate improvements (10–30%), and 21.8% did not respond ($p < 0.01$). They found that younger patients with a shorter history of Parkinson's disease had a better chance of responding and displaying significant disability improvements than older patients and patients with a longer duration of disease. No difference was found between the oral NADH and the IV NADH (Birkmayer et al. (1993). However, when Dizdar et al. (1994) repeated this study with a similar trial, they found no statistically significant improvements in Parkinson's disease symptom scores.

Stabilized, oral NADH has also been used to reduce symptoms in CFS patients and in patients with chronic fatigue. For example, CFS patients were given stabilized, microencapsulated, oral NADH or placebo for 4 weeks in a blinded crossover trial (Forsyth et al. 1999). In this clinical study 8/26 (30.7%) patients responded to the NADH compared with 2 of 26 (8%) in the placebo arm ($p < 0.05$). Thus these results were not considered significant by Colquhoun and Senn (2000). In another clinical trial using CFS patients oral, stabilized NADH was compared to psychological/nutritional therapy. The stabilized NADH reduced fatigue in the first 4 months of a 12 month trial. However, after the first 4 months, symptom scores were similar in the NADH and psychological/nutritional arms of the trial (Santaella et al. 2004). In an open label study stabilized NADH was given orally for 2 months to CFS patients (Alegre et al. 2010). They found decreases in anxiety and maximum heart rate after a stress test, but no differences were found in the functional impact of fatigue, quality of life, sleep quality, exercise capacity, or functional reserve (Alegre et al. 2010). The clinical studies described above suggest mixed results with stabilized NADH. Some patients responded to the oral, stabilized NADH, but others did not.

6 Combination Natural Supplements and Mitochondrial Dysfunction

There are a few examples of using combinations of MLR supplements to reduce the effects of mitochondrial dysfunction. Ellithorpe et al. (2003) used a membrane phospholipid-vitamin mixture (Propax™ with NTFactor®, various vitamins and minerals) to treat aging patients with severe chronic fatigue. They found reductions in overall fatigue of 40.5% within 8 weeks. Examination of the subcategories of fatigue in this study indicated that the combination MLR supplement reduced all subcategories of fatigue, such as the behavioral/severity, affective/meaning, sensory, and cognitive/mood dimensions of fatigue. This same oral supplement was used to reduce cancer-associated fatigue and the fatigue-effects of cancer therapy (Colodny et al. 2001). For example, Propax™ reduced chemotherapy-induced fatigue, nausea, vomiting, malaise, diarrhea, headaches and other side effects of cancer therapy. Eighty-one percent of the patients on chemotherapy that used the combination MLR supplement experienced an overall improvement in quality of

life parameters. In a subsequent double-blind, placebo-controlled cross-over trial 36 patients on chemotherapy plus Propax™ showed fewer adverse effects, resulting in improvements in fatigue, nausea, diarrhea, impaired taste, constipation, insomnia and other quality of life indicators (Colodny et al. 2001).

In a study using long-term intractable fatigue patients with a variety of diagnoses a MLR supplement containing membrane glycerolphospholipids, CoQ10, microencapsulated NADH, alpha-Lipoic acid, L-carnitine, alpha-Ketoglutaric acid and other nutrients (ATP Fuel®) was to treat fatigue and mitochondrial dysfunction (Nicolson et al. 2012a). The 58 participants in this trial had moderate to severe intractable fatigue for an average of more than 17 years and had seen an average of more than 15 practitioners without resolution of their fatigue. These patients had tried unsuccessfully an average of over 35 drugs and supplements to reduce their fatigue without success.

The chronic illness patients in the ATP Fuel® trial took the combination oral MLR supplement for 8 weeks, and fatigue was determined at several intermediate end points during and at the end of the trial. After 8 weeks of supplement the mean fatigue scores improved by 30.7% (t-test, $p < 0.0001$ and Wilcoxon signed-rank, $p < 0.0001$) (Nicolson et al. 2012a). The fatigue scores were further dissected into four fatigue 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 the subcategories showed significant reductions by the end of the trial ($p < 0.0001$) (Nicolson et al. 2012a).

Regression analysis was used to determine if the downward trends in fatigue over time during the ATP Fuel® trial were consistent, occurred with a high degree of confidence, and could predict further reductions in fatigue. The regression analyses of overall fatigue and each of the subcategories of fatigue indicated significant and consistent downward trends in the fatigue data. The regression R^2 values for the various subgroups varied from 0.950 to 0.980. Regression analysis of the overall fatigue yielded a R^2 of 0.960. This indicated that there was a high level of confidence and reproducibility in the downward trends in all fatigue data. The combination MLR supplement was safe, and there were no safety issues that came up during the trial (Nicolson et al. 2012a). Separately Lyme patients were examined to see if they responded with decreases in fatigue while on ATP Fuel® (Nicolson et al. 2012b). Similar to the study on intractable fatigue patients, the Lyme disease patients also showed dignificant reductions in overall fatigue and in all fatigue subcategories during an 8-week open label trial using ATP Fuel® (Nicolson et al. 2012b).

7 Other Natural Supplements That Have Not Been Extensively Tested

One natural supplement that has stimulated attention because of its effects on mitochondria is pyrroloquinoline quinone (PQQ). PQQ is a redox cofactor that displays anti-oxidant, anti-inflammatory and neuroprotective effects by modulating mitochondrial lipid and energy metabolism (Lee et al. 2014; Tao et al. 2007; Yang et al. 2014; Zhang et al. 2012). It also acts as a growth factor or even vitamin in laboratory animals (Bauerly et al. 2011; Killgore et al. 1989; Rucker et al. 2009; Steinberg et al. 1994), although it appears that PQQ does not meet the criteria for a vitamin (Felton and Anthony 2005). PQQ modifies the quantity and function of mitochondria in mice, such as promoting the spontaneous generation of new mitochondria in aging cells—thus it appears to be a stimulator of mitochondrial biogenesis (Chowandisai et al. 2010; Stites et al. 2006).

PQQ occurs normally in human tissues, and some (100–400 ng/day) is thought to be synthesized in humans (Harris et al. 2013). It is also found in various foods at different concentrations (Kumazawa et al. 1995). PQQ is thought to induce mitochondrial biogenesis through a cell signaling mechanism mediated through activation of specific nuclear and mitochondrial transcription pathways (Chowandisai et al. 2010).

Although PQQ is now available as a commercial supplement, there are few clinical studies in the literature on its effectiveness in promoting mitochondrial function in humans. Using PQQ as a dietary supplement does appear to be safe. Harris et al. (2013) used a placebo-controlled cross-over study to examine the effects of PQQ on pathways of inflammation, lipid and carbohydrate metabolism and urinary metabolites that are related to oxidative damage. After 76 h they found some changes in their measurements on markers of inflammation (C-reactive protein, interleukin-6), other blood markers (cholesterol, glucose, high- and low-density lipoproteins, triglycerides and other markers) and urinary metablolites by ^{1}H-nuclear magnetic resonance. Although the standard clinical markers were not altered by PQQ supplementation, there were significant reductions in C-reactive protein, interleukin-6 and urinary methylated amines consistent with reductions in inflammation as well as changes in antioxidant potential and enhancement in mitochondria-related functions. Additional studies will be need to confirm these findings and expand the effects to include other clinical aspects of mitochondrial function.

8 Final Comment

Oral mitochondrial supplements, such as the use of all-natural membrane glycerol phospholipids with or without other supplements and nutrients, can increase mitochondrial function and reduce fatigue and other symptoms and improve quality of life in patients with chronic illnesses. Future studies will concentrate on the use of

MLR supplements to improve clinical symptoms in a variety of chronic illnesses. For example, based on preliminary studies we have initiated a new double-blinded, placebo-conrolled, cross-over clinical trial using fibromyalgia patients to assess the use of NTFactor Lipids® in reducing pain, fatigue, gastrointestinal and other symptoms. Future studies will need to carefully document the effectiveness of natural supplements using randomized, controlled clinical trials.

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