Enhancing Energy Levels Through Mitochondrial Support

By Nieske Zabriskie, ND Surveys have shown that almost one-third of adults report having fatigue,[1] and 24 percent of patients report that their fatigue is a major health problem.[2] Many scientists believe that one cause of fatigue is mitochondrial dysfunction.[3] Mitochondria are structures within cells primarily responsible for energy production. The mitochondria are often referred to as the powerhouse of the cell, and are responsible for cellular respiration and the resulting generation of adenosine tri-phosphate (**ATP**). ATP is the chemical energy currency in the cell. The body produces an amazing 50 to 75 kg of ATP per day.[4] There are three main pathways used to generate energy: cellular respiration including glycolysis and the citric acid cycle, oxidative phosphorylation, and beta-oxidation. Mitochondrial dysfunction results in decreased ATP production and thus, may lead to fatigue.

Aging, Fatigue, and Mitochondrial Function

Normal mitochondrial function is imperative for optimal energy production. Aging cells have a diminished ability to produce ATP due to changes in mitochondrial structure and function. Aging has been shown to decrease the efficiency of mitochondrial oxidative phosphorylation, which provides the majority of ATP production. Aging also increases the production of damaging free radicals such as reactive oxygen species (ROS) in the mitochondria.[5] Cells have several antioxidant enzymes to remove excess ROS from causing damage; however, these enzymes, as well as the enzymes required for oxidative phosphorylation, decrease with age.[6] Mitochondria have their own DNA, and research indicates that mitochondrial DNA mutations begin accumulating in cells in individuals after the mid-thirties,[7] which contributes to the decreased ATP production and increased levels of ROS seen with increasing age.[8] Also, researchers have shown that the loss of muscle mass and function seen with aging is associated with mitochondrial damage in muscle cells.[9]

Numerous diseases are associated with mitochondrial dysfunction such as Parkinson's disease, Alzheimer's disease, coronary artery disease, chronic fatigue syndrome (CFS), fibromyalgia, and diabetes, among others.[10] Fatigue, in particular, is associated with mitochondrial dysfunction. One study found that muscle biopsies indicate that post-viral fatigue syndrome may be due to mitochondrial dysfunction precipitated by a virus infection.[11] Evidence also indicates that fatigue seen in other conditions such as metabolic syndrome is due to excess cellular oxidative stress caused by free radicals leading to oxidative damage to mitochondria, and resulting in reduced efficiency of mitochondrial energy production.[12] Studies have also shown that patients suffering with chronic fatigue have improved with supplementation of mitochondrial nutrients and **antioxidants**, showing a reduction in damage to mitochondrial membranes, restoring mitochondrial energy production, protecting cellular structures and enzymes from oxidative damage, and decreasing fatigue.[13]

Nutrients to Support Mitochondrial Function

While there are a number of nutrients shown to improve various aspects of mitochondrial function, there are seven nutrients that can be especially effective and act synergistically to improve mitochondrial function. These seven nutrients are **L-carnitine**, **lipoic acid**, **N-acetyl cysteine**, succinic acid, EDTA, plus **D-ribose**, and **Coenzyme Q10**.

Carnitine plays an important role in fatty acid metabolism and is essential for mitochondrial energy production. Acetyl-L-carnitine is a derivative of carnitine and is a precursor to the molecule acetyl coenzyme A, important in the citric acid cycle. N-acetyl-carnitine also assists in the transportation of long-chain fatty acids into the mitochondria for beta-oxidation. Beta-oxidation is the process in which fatty acids are broken down in mitochondria to generate Acetyl-CoA, the entry molecule for the citric acid cycle. The carnitines also have significant antioxidant activity, providing a protective effect against lipid peroxidation and oxidative stress.

TABLE 1. Fatigue-Fighting Nutrients

L-Carnitine	Patients with chronic fatigue syndrome have significantly lower levels of serum acetyl l carnitine, total carnitine, and free carnitine.
Lipoic Acid	Protects and repairs age-induced mitochondrial DNA damage, thereby up-regulating mitochondrial function and improving energy production.
N-Acetyl Cysteine (NAC)	Directly improves mitochondrial energy production efficiency.
D-Ribose	In patients with fibromyalgia and/or chronic fatigue syndrome, supplementation with this five-carbon sugar has resulted in increased energy and overall well-being.
Coenzyme Q10 (CoQ10)	Decreases with age, which may contribute to age-related mitochondrial dysfunctions; Shown to decrease fatigue after physical activity and improve energy levels of chronic fatigue patients.
Succinate (succinic acid)	Helps support the health of patients with mitochondrial defects.
EDTA	Works with the above nutrients to stabilize mitochondrial membranes.

Researchers have shown that patients with chronic fatigue syndrome have significantly lower levels of serum acylcarnitine, total carnitine, and free carnitine. Additionally, the study showed that serum levels of total and free carnitine correlated with the clinical presentation, as higher carnitine levels correlated with better functional capacity.[14] Similar studies also showed that the concentration of serum

acylcarnitine in patients with chronic fatigue syndrome (CFS) tended to increase to normal levels with the recovery of general fatigue.[15] These studies suggest that mitochondrial dysfunction may contribute to or cause the symptoms of general fatigue, myalgia, muscle weakness, and post-exertional malaise in patients with CFS. In addition, numerous cardiovascular diseases exhibit similar energy metabolism dysfunction in that ATP synthesis is decreased due to inadequate fatty-acid fuels delivery to the mitochondria, and L-carnitine levels are decreased in these diseases.[16]

Lipoic acid is a potent antioxidant and has the ability to protect and repair age-induced mitochondrial DNA damage, thereby up-regulating mitochondrial function and improving energy production.[17] Animal studies have shown that supplementation with lipoic acid has dramatic effects on improving age-related declines in mitochondrial function. Lipoic acid reverses the decline in oxygen consumption, increases mitochondrial membrane potential, decreases levels of ROS and markers of lipid peroxidation, increases ambulatory activity and improves the age-associated decline of memory, increases the levels of antioxidants, and restores the activity of key enzymes.[18] Interestingly, numerous studies have shown that acetyl-L-carnitine in combination with lipoic acid increases cellular metabolism and lowers oxidative stress better than either compound alone.[19]

N-acetyl cysteine (NAC) is a precursor for glutathione, a potent antioxidant, and stimulates the enzymes involved in glutathione regeneration. NAC also exhibits antioxidant properties of its own, counteracting the effects of reactive ROS and protecting mitochondrial proteins from damage. NAC has been shown to prevent programmed cell death (apoptosis) in cultured nerve cells and increases activity of mitochondrial complex proteins.[20-21] Additional studies have demonstrated that NAC supplementation decreased age-related memory loss, with decreased levels of oxidants in mice.[22] Research also indicates that NAC supplementation directly improves mitochondrial energy production efficiency.[23]

Ribose is a five-carbon sugar used by all living cells and is an essential component for energy production. Ribose provides the necessary substrate for synthesis of nucleotides, which form major cellular components such as ATP. The availability of ribose determines the rate at which these nucleotides can be made by the cells. In one study, D-ribose was supplemented to patients with fibromyalgia and/or chronic fatigue syndrome at a dose of 5 grams three times daily. Compared to baseline, patients reported significant improvement in all five categories measured including energy, pain intensity, sleep, mental clarity, and well-being with D-ribose supplementation. In fact, 66 percent of patients reported significant improvement, with an average increase in energy of 45 percent, and an average improvement in overall well-being of 30 percent.[24] Research also indicates that in muscle, ribose can accelerate ATP synthesis by up to 4.3-fold and increase energy salvage by up to 8-fold, which is important for muscle function and athletic performance.[25] In addition, pre- and post-exercise supplementation with D-ribose decreases free radical formation.[26]

Coenzyme Q10 (CoQ10) is a compound made by the body and primarily functions as an antioxidant, membrane stabilizer, and a cofactor in cellular respiration. CoQ10 is

important in oxidative phosphorylation, and found in highest levels in the cells with the greatest energy demand, the heart and liver. CoQ10 decreases with age, which may contribute to age-related mitochondrial dysfunctions. In one study, researchers showed that in patients with chronic fatigue of unknown etiology for at least 6 months, 69 percent reported improvement with CoQ10 supplementation.[27] CoQ10 has also been shown to alleviate fatigue, improve physical performance, and decrease the recovery period with fatigue-inducing physical activity.[28]

Another substance important for mitochondrial health is succinate (succinic acid), a citric acid cycle intermediate, in which succinate is converted to fumarate. Supplementation with succinate has shown benefit in patients with mitochondrial defects.[29] Finally, EDTA can be used with all of the nutrients mentioned above to stabilize mitochondrial membranes.

Conclusion

Fatigue is a common complaint and presents with numerous medical conditions. However, optimizing mitochondrial function improves energy production, and may help alleviate fatigue. Nutrients such as L-carnitine, lipoic acid, N-acetyl-cysteine, succinate, and EDTA, combined with D-ribose and CoQ10 have all been shown to improve mitochondrial energy production.

References: 1. Bates DW, Schmitt W, Buchwald D, et al. Prevalence of fatigue and chronic fatigue syndrome in a primary care practice. Arch Intern Med. 1993 Dec 27;153(24):2759-65.

2. Kroenke K, Wood DR, Mangelsdorff AD, et al. Chronic fatigue in primary care. Prevalence, patient characteristics, and outcome. JAMA. 1988 Aug 19;260(7):929-34.

3. Bains W. Treating Chronic Fatigue states as a disease of the regulation of energy metabolism. Med Hypotheses. 2008 Oct;71(4):481-8.

4. Di Carlo SE, Coliins HL. Submitting illuminations for review. Advan Physiol Edu. 2001;25:70–71.

5. Lesnefsky EJ, Hoppel CL. Oxidative phosphorylation and aging. Ageing Res Rev. 2006 Nov;5(4):402-33.

6. Cortopassi GA, Wong A. Mitochondria in organismal aging and degeneration. Biochim Biophys Acta. 1999 Feb 9;1410(2):183-93.

7. Fahn HJ, Wang LS, Hsieh RH, et al. Age-related 4,977 bp deletion in human lung mitochondrial DNA. Am J Respir Crit Care Med. 1996 Oct;154(4 Pt 1):1141-5.

8. Wei YH, Lee HC. Oxidative stress, mitochondrial DNA mutation, and impairment of antioxidant enzymes in aging. Exp Biol Med (Maywood). 2002 Oct;227(9):671-82.

9. Dirks AJ, Hofer T, Marzetti E, et al. Mitochondrial DNA mutations, energy metabolism and apoptosis in aging muscle. Ageing Res Rev. 2006 May;5(2):179-95.

10. Pieczenik SR, Neustadt J. Mitochondrial dysfunction and molecular pathways of disease. Exp Mol Pathol. 2007 Aug;83(1):84-92.

11. Behan WM, More IA, Behan PO. Mitochondrial abnormalities in the postviral fatigue syndrome. Acta Neuropathol. 1991;83(1):61-5.

12. Nicolson GL. Metabolic syndrome and mitochondrial function: molecular replacement and antioxidant supplements to prevent membrane peroxidation and restore mitochondrial function. J Cell Biochem. 2007 Apr 15;100(6):1352-69.

13. Nicolson GL, Conklin KA. Reversing mitochondrial dysfunction, fatigue and the adverse effects of chemotherapy of metastatic disease by molecular replacement therapy. Clin Exp Metastasis. 2008;25(2):161-9.

14. Plioplys AV, Plioplys S. Serum levels of carnitine in chronic fatigue syndrome: clinical correlates. Neuropsychobiology. 1995;32(3):132-8.

15. Kuratsune H, Yamaguti K, Takahashi M, et al. Acylcarnitine deficiency in chronic fatigue syndrome. Clin Infect Dis. 1994 Jan;18 Suppl 1:S62-7.

16. Carvajal K, Moreno-Sanchez R. Heart metabolic disturbances in cardiovascular diseases. Arch Med Res. 2003;34:89–99.

17. McCarty MF, Barroso-Aranda J, Contreras F. The "rejuvenatory" impact of lipoic acid on mitochondrial function in aging rats may reflect induction and activation of PPAR-gamma coactivator-1alpha. Med Hypotheses. 2009 Jan;72(1):29-33.

18. Hagen TM, Ingersoll RT, Lykkesfeldt J, et al. (R)-alpha-lipoic acid-supplemented old rats have improved mitochondrial function, decreased oxidative damage, and increased metabolic rate. FASEB J. 1999 Feb;13(2):411-8.

19. Liu J. The effects and mechanisms of mitochondrial nutrient alpha-lipoic acid on improving age-associated mitochondrial and cognitive dysfunction: an overview. Neurochem Res. 2008 Jan;33(1):194-203.

20. Banaclocha MM. Therapeutic potential of N-acetylcysteine in age-related mitochondrial neurodegenerative diseases. Med Hypotheses. 2001 Apr;56(4):472-7.

21. Nicoletti VG, Marino VM, Cuppari C, et al. Effect of antioxidant diets on mitochondrial gene expression in rat brain during aging. Neurochem Res. 2005 Jun-Jul;30(6-7):737-52.

22. Martínez M, Hernández AI, Martínez N. N-Acetylcysteine delays age-associated memory impairment in mice: role in synaptic mitochondria. Brain Res. 2000 Feb 7;855(1):100-6.

23. Cocco T, Sgobbo P, Clemente M, et al. Tissue-specific changes of mitochondrial functions in aged rats: effect of a long-term dietary treatment with N-acetylcysteine. Free Radic Biol Med. 2005 Mar 15;38(6):796-805.

24. Teitelbaum JE, Johnson C, St Cyr J. The use of D-ribose in chronic fatigue syndrome and fibromyalgia: a pilot study. J Altern Complement Med. 2006;12(9):857-62.

25. Hellsten Y, Skadhauge L, Bangsbo J. Effect of Ribose Supplementation on Resynthesis of Adenine Nucleotides after Intermittent Training in Humans. AM J Physiol, Regul Intergr Comp Physiol. 2004;286:R182-R188.

26. Seifert JG, Subhudi A, Fu M-X, et al. The Effects of Ribose Ingestion on Indicies or Free Radical Production During Hypoxic Exercise. Free Rad Biol Med. 2002;33(Suppl 1):S269.

27. Bentler SE, Hartz AJ, Kuhn EM. Prospective observational study of treatments for unexplained chronic fatigue. J Clin Psychiatry. 2005 May;66(5):625-32.

28. Mizuno K, Tanaka M, Nozaki S, et al. Antifatigue effects of coenzyme Q10 during physical fatigue. Nutrition. 2008 Apr;24(4):293-9.

29. Shoffner JM, Lott MT, Voljavec AS, et al. Spontaneous Kearns-Sayre/chronic external ophthalmoplegia plus syndrome associated with a mitochondrial DNA deletion: a slip-replication model and metabolic therapy. Proc Natl Acad Sci USA. 1989

Energizing sick mitochondria with vitamin B3: Effective treatment for mitochondrial disease

The researchers of the University of Helsinki, Finland, and École Polytechnique Fédérale de Lausanne, Switzerland, have shown that vitamin **B3 form nicotinamide riboside can slow down the progression of mitochondrial disease, suggesting its potential as a novel therapy approach to adult-onset mitochondrial muscle diseases**[F1].--Vitamins B have recently been turned out to be potent modifiers of energy metabolism, especially the function of mitochondria**. Vitamin B3, (niacin) has been found to delay the signs of aging in animal models**.--An international collaboration between the University of Helsinki and École Polytechnique Fédérale de Lausanne reported today in the journal *Embo Molecular Medicine* **that vitamin B3 form, nicotinamide riboside**[F2], **can slow down the progression of mitochondrial disease, suggesting its potential as a novel**

therapy approach to adult-onset mitochondrial muscle diseases.-- **Mitochondria power up all cells in our bodies, by generating fuel, ATP, for all cellular functions**. Dysfunction of these cellular engines can cause mitochondrial disorders, which are the most common cause of inherited metabolic diseases in adults and children. **Mitochondrial myopathy is the most frequent form of adult mitochondrial disorder. The typical symptoms in the patients are muscle weakness, pain and cramps. Despite the progressive nature of these diseases, no curative treatment is available**.

In their current publication, Dr Nahid Khan in Prof Anu Suomalainen Wartiovaara's group showed **that feeding mice with food supplemented with B3 form, nicotinamide riboside, delayed their mitochondrial myopathy**. **The treatment increased mitochondrial mass and function, and cured the structural abnormalities**. **These results clearly showed the potential of this vitamin B form, a natural constituent of milk, to activate dysfunctional mitochondrial metabolism."** These results are a breakthrough for understanding the mechanisms of human mitochondrial muscle diseases and for exploring the efficient treatment options for these progressive disorders of adults. **They also highlight the potent role of niacin in guiding mitochondrial energy metabolism**," Professor Anu Suomalainen Wartiovaara states.

Story Source-The above post is reprinted from materials provided by **Helsingin yliopisto (University of Helsinki)**.

Journal Reference-Nahid A Khan, Mari Auranen, Ilse Paetau, Eija Pirinen, Liliya Euro, Saara Forsström, Lotta Pasila, Vidya Velagapudi, Christopher J Carroll, Johan Auwerx and Anu Suomalainen. **Effective treatment of mitochondrial myopathy by nicotinamide riboside, a vitamin B3**. *EMBO Molecular Medicine*, April 2014 DOI: 10.1002/emmm.201403943

Helsingin yliopisto (University of Helsinki). "Energizing sick mitochondria with vitamin B3: Effective treatment for mitochondrial disease." ScienceDaily. ScienceDaily, 7 April 2014. <www.sciencedaily.com/releases/2014/04/140407090403.htm>.