

MITO 101 – Exercise and Prevention

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Exercise

- Many patients with mitochondrial cytopathy have very low maximal oxygen uptakes (VO_{2peak})¹, which can limit even the performance of activities of daily living.
- Despite their subjective exercise intolerance, many patients report improvement following formal exercise programs. Initially, a patient may feel more tired when starting an exercise program and longer rest periods may be required until the body adapts to the stress. More sleep, optimal nutritional timing and hydration (see below), and a reduction in other stressors (where possible) may limit some of the initial fatigue experienced when first starting an exercise program.
- Strength is often less affected, but can be decreased in the presence of neuropathy, with more severe muscle involvement, and through de-conditioning.
- Studies have found that graded endurance exercise is tolerated by patients with mitochondrial disease, improves exercise capacity and mitochondrial enzyme activity, and does not increase the mutational burden^{2,3}.
- Resistance exercise (weights) can be performed by many patients and can increase strength, but the number of reported cases is small^{1,4}. In theory, resistance exercise should be fairly well tolerated since it relies on the anaerobic energy systems. In sporadic mitochondrial disorders, there may be recruitment of satellite cells with relatively lower mutational burdens, resulting in a downshift of the overall mutational load in the whole muscle⁴.
- Patients should be evaluated prior to exercise training with an exercise test using a 12-lead ECG and a metabolic cart. Since some of the mitochondrial disorders result in cardiomyopathy, an echocardiogram should also be done, if it has not already been performed.
- Patients should follow general principles of exercise training including: (i) start at very low intensities and duration and progress gradually; (ii) listen to their bodies and take more time off if the muscles are still fatigued and sore. Patients should not exercise the same muscle group on back-to-back days, and make sure that a trained professional (kinesiologist or certified trainer) teaches technique and monitors the initial progression.
- We have found that a reclining cycle is much better tolerated in patients with more severe mitochondrial disease, especially those with ataxia.
- Exercise should be supervised or done with a partner, especially in those patients who have seizure disorders.
- Whenever possible, exercise should be completed at a temperature that is neither too hot nor too cold. Cold environments can be usually dealt with using proper layering of clothing, while hot environments are more challenging and require careful consideration of many factors, including clothing, temperature, humidity and hydration status (see also the American College of Sports Medicine (ACSM) link provided below for further information).
- Never exercise during concomitant illness or in the fasted state. Most people benefit from ~ 250 mL of a carbohydrate drink ~ 20 minutes before a work-out (e.g. sport drink, juice diluted 50 % with water). The ACSM has free guidelines and position statements on a wide variety of topics such as; fluid replacement, exercise and type 2 diabetes and other issues: <http://www.acsm->

msse.org/pt/re/msse/positionstandards.htm?sessionid=Hbgp1xR65pjzyqL4Lm0fjCMty9hrccQJyB6grfkWh5v8yRw1mrsT!1899110359!181195628!8091!-1).

Prevention

- A ketogenic diet may be used for intractable seizures and this is not contraindicated in mitochondrial disease, particularly with complex I deficiency⁵. Ketogenic or other high fat diets are not recommended for long-term consumption due to the potential for cardiovascular risks, such as ischemic heart disease and other atherosclerotic issues.
- Smoking is definitely contraindicated in mitochondrial disease because carbon monoxide reduces oxygen delivery to the cell and because of other serious effects (cancer risk, cardiovascular disease). Patients should be counseled and supported to quit. Patients with Leber's Hereditary Optic Neuropathy may be particularly sensitive to the deleterious effects of smoking^{6,7}. Recent work has also found that nicotine itself can inhibit mitochondrial function^{8,9}; consequently, the use of nicotine gum and patches is not recommended.
- Many patients report an intolerance to alcohol and consumption beyond government guidelines should be curtailed due to nutrient displacement (7 kcal/g), thiamine depletion, and direct cellular toxicity/oxidative stress^{7,10}.
- Although some over-the-counter supplements may be of therapeutic utility in mitochondrial cytopathies (see section on Supplements and Nutrition), some compounds may be deleterious, including ephedra¹¹, and it is likely that other weight-loss compounds may also increase metabolic demand and should only be used under medical supervision and with a high level of caution. Illicit drugs that increase metabolism such as ecstasy, amphetamines and cocaine are also expectedly deleterious to mitochondrial function and should be avoided^{12,13}.
- If hypercholesterolemia is identified or cholesterol reduction is indicated (e.g. post MI), a drug that inhibits fat absorption (e.g. cholestyramine or ezetimibe) may be safest. Fibric acid drug may improve fatty acid oxidation¹⁴, but may impair complex I activity¹⁵. A statin should be used only with simultaneous CoQ10 and L-carnitine supplementation¹⁶, and only after weighing the risk/benefit ratio.
- Alterations in thyroid function can negatively impact mitochondrial function¹⁷. Prompt recognition and treatment of hypothyroidism (more common) and hyperthyroidism (less common) is important.
- Medications used in the treatment of HIV infection are toxic to the mitochondria and must be used only with extreme caution in patients with co-existent mitochondrial disease^{18,19}.
- Treatment of type 2 diabetes (T2DM) is fine with insulin and drugs such as glyburide also appear to be safe. The thiazolidendiones appear to be safe in mitochondrial disease and may be neuroprotective²⁰ and increase mitochondrial number²¹; however, they may also lead to abnormal mitochondrial inclusions²². Because of questions about long-term cardiac safety²³, the use of thiazolidendiones in mitochondrial disease patients remains questionable. Metformin can lead to lactic acidosis (MALA = Metformin-induced Lactic Acidosis)²⁴, and is definitely contraindicated in mitochondrial disease. Alpha-lipoic acid should be part of a supplement

cocktail if a patient has T2DM ²⁵⁻²⁷, (see also section on Supplements and Nutrition).

- Physiological stressors should be avoided, including - but not limited to -: hyperthermia (fever, environment), hypothermia (environment), excessive exercise, and starvation (npo for surgery – ensure that there is a source of parenteral glucose under such conditions).
- Treatment of fever should NEVER include ASA in children and rarely, if ever, in adults due to mitochondrial toxicity ²⁸.
- Adequate sleep should be considered in fatigued patients and a sleep study may be advisable to identify treatable conditions such as apnea, hypoxemia, restless legs syndrome, nocturnal myoclonus or seizures.

Table 1. Medications to avoid in patients with mitochondrial disorders.

<u>Compound</u>	<u>Rationale</u>
Statins	May deplete CoQ10.
HIV medications	Inhibit polymerase gamma (mtDNA depletion).
ASA	Inhibit mitochondrial function. Reye disease in children.
Valproic acid	Liver toxicity, deplete carnitine.
Metformin	Lactic acidosis due to mitochondrial impairment.
Alcohol	Increase oxidative stress, mitochondrial toxin.
Smoking (nicotine).	Inhibit complex IV, damage mitochondria
Cocaine, amphetamine, ecstasy	Increase metabolic demand on cells.

References

1. Taivassalo T, Haller RG. Exercise and training in mitochondrial myopathies. *Med Sci Sports Exerc* 2005;37:2094-101.
2. Taivassalo T, Gardner JL, Taylor RW, et al. Endurance training and detraining in mitochondrial myopathies due to single large-scale mtDNA deletions. *Brain* 2006;129:3391-401.
3. Jeppesen TD, Schwartz M, Olsen DB, et al. Aerobic training is safe and improves exercise capacity in patients with mitochondrial myopathy. *Brain* 2006;129:3402-12.
4. Taivassalo T, Fu K, Johns T, Arnold D, Karpati G, Shoubridge EA. Gene shifting: a novel therapy for mitochondrial myopathy. *Hum Mol Genet* 1999;8:1047-52.
5. Roef MJ, de Meer K, Reijngoud DJ, et al. Triacylglycerol infusion improves exercise endurance in patients with mitochondrial myopathy due to complex I deficiency. *Am J Clin Nutr* 2002;75:237-44.
6. Sadun AA, Carelli V, Salomao SR, et al. Extensive investigation of a large Brazilian pedigree of 11778/haplogroup J Leber hereditary optic neuropathy. *Am J Ophthalmol* 2003;136:231-8.
7. Charlmers RM, Harding AE. A case-control study of Leber's hereditary optic neuropathy. *Brain* 1996;119 (Pt 5):1481-6.
8. Holloway AC, Cuu DQ, Morrison KM, Gerstein HC, Tarnopolsky MA. Transgenerational effects of fetal and neonatal exposure to nicotine. *Endocrine* 2007;31:254-9.
9. Cormier A, Morin C, Zini R, Tillement JP, Lagrue G. In vitro effects of nicotine on mitochondrial respiration and superoxide anion generation. *Brain Res* 2001;900:72-9.
10. Sadun A. Acquired mitochondrial impairment as a cause of optic nerve disease. *Trans Am Ophthalmol Soc* 1998;96:881-923.
11. Warner RB, Lee AG. Leber hereditary optic neuropathy associated with use of ephedra alkaloids. *Am J Ophthalmol* 2002;134:918-20.
12. Cunha-Oliveira T, Rego AC, Cardoso SM, et al. Mitochondrial dysfunction and caspase activation in rat cortical neurons treated with cocaine or amphetamine. *Brain Res* 2006;1089:44-54.
13. Cardaioli E, Da Pozzo P, Gallus GN, et al. Leber's hereditary optic neuropathy associated with cocaine, ecstasy and telithromycin consumption. *J Neurol* 2007;254:255-6.
14. Djouadi F, Aubey F, Schlemmer D, et al. Bezafibrate increases very-long-chain acyl-CoA dehydrogenase protein and mRNA expression in deficient fibroblasts and is a potential therapy for fatty acid oxidation disorders. *Hum Mol Genet* 2005;14:2695-703.
15. Scatena R, Bottoni P, Vincenzoni F, et al. Bezafibrate induces a mitochondrial derangement in human cell lines: a PPAR-independent mechanism for a peroxisome proliferator. *Chem Res Toxicol* 2003;16:1440-7.
16. Vladutiu GD, Simmons Z, Isackson PJ, et al. Genetic risk factors associated with lipid-lowering drug-induced myopathies. *Muscle Nerve* 2006;34:153-62.

17. Zoll J, Ventura-Clapier R, Serrurier B, Bigard AX. Response of mitochondrial function to hypothyroidism in normal and regenerated rat skeletal muscle. *J Muscle Res Cell Motil* 2001;22:141-7.
18. Venhoff N, Setzer B, Melkaoui K, Walker UA. Mitochondrial toxicity of tenofovir, emtricitabine and abacavir alone and in combination with additional nucleoside reverse transcriptase inhibitors. *Antivir Ther* 2007;12:1075-85.
19. Blanco F, Garcia-Benayas T, Jose de la Cruz J, Gonzalez-Lahoz J, Soriano V. First-line therapy and mitochondrial damage: different nucleosides, different findings. *HIV Clin Trials* 2003;4:11-9.
20. Jung TW, Lee JY, Shim WS, et al. Rosiglitazone protects human neuroblastoma SH-SY5Y cells against acetaldehyde-induced cytotoxicity. *Biochem Biophys Res Commun* 2006;340:221-7.
21. Strum JC, Shehee R, Virley D, et al. Rosiglitazone induces mitochondrial biogenesis in mouse brain. *J Alzheimers Dis* 2007;11:45-51.
22. Caldwell SH, Patrie JT, Brunt EM, et al. The effects of 48 weeks of rosiglitazone on hepatocyte mitochondria in human nonalcoholic steatohepatitis. *Hepatology* 2007;46:1101-7.
23. Lindberg M, Astrup A. The role of glitazones in management of type 2 diabetes. A dream or a nightmare? *Obes Rev* 2007;8:381-4.
24. Spiller HA, Sawyer TS. Toxicology of oral antidiabetic medications. *Am J Health Syst Pharm* 2006;63:929-38.
25. Foster TS. Efficacy and safety of alpha-lipoic acid supplementation in the treatment of symptomatic diabetic neuropathy. *Diabetes Educ* 2007;33:111-7.
26. Kamenova P. Improvement of insulin sensitivity in patients with type 2 diabetes mellitus after oral administration of alpha-lipoic acid. *Hormones (Athens)* 2006;5:251-8.
27. Ziegler D. Treatment of diabetic polyneuropathy: Update 2006. *Ann N Y Acad Sci* 2006;1084:250-66.
28. Gutknecht J. Aspirin, acetaminophen and proton transport through phospholipid bilayers and mitochondrial membranes. *Mol Cell Biochem* 1992;114:3-8.