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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 performance in activities of daily living and exercise.
- Despite their subjective exercise intolerance, many patients report less fatigue 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 patients can be weak in the presence of neuropathy, in those with more severe muscle involvement, and through de-conditioning.
- Studies have found that a progressive endurance exercise program improves exercise capacity and mitochondrial enzyme activity, does not increase the mutational burden, and is well tolerated by patients with mitochondrial disease [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; however, the recovery between bouts is aerobic and long rest periods may be required (normal = 2 minutes between sets of exercise; may need to increase to up to 5 minutes). 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 muscle [4].
- Patients should be evaluated prior to all forms of 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 in the past.
- Patients should follow the 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. As mentioned above, a 2 minute rest period between exercising the same muscle group is the usual recommendation to allow for phosphocreatine re-synthesis and this may need to be extended for up to 5 minutes in a patient with mitochondrial disease).
- Most studies have shown that creatine monohydrate supplementation enhances the strength and mass gains during resistance exercise training [5, 6], and should be considered in mitochondrial disease patients performing resistance training (see Revised Mito 101 section on Supplements and Nutrition).
- 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;jsessionid=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 deficiency[7]. 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 [8, 9]. Recent work has also found that nicotine itself can inhibit mitochondrial function [10, 11]; consequently, the use of nicotine gum and patches is not recommended and other anti-smoking methods are 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 [9, 12].
- Although some over-the-counter supplements may be of therapeutic utility in mitochondrial cytopathies (see Revised Mito 101 section on Supplements and Nutrition), some compounds may be deleterious, including ephedra [13], 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 [14, 15].
- If hypercholesterolemia is identified or cholesterol reduction is indicated (e.g. post MI), a drug that inhibits fat absorption (e.g. cholestyramine or eztitimbe) may be safest. Fibric acid drug may improve fatty acid oxidation[16], but may impair complex I activity[17]. A statin should be used only with simultaneous CoQ10 and L-carnitine supplementation[18], and only after weighing the risk/benefit ratio.

- Alterations in thyroid function can negatively impact mitochondrial function [19]. 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 [20, 21].
- Treatment of type 2 diabetes (T2DM) is fine with insulin and drugs such as glyburide also appear to be safe. The thiazoladendiones appear to be safe in mitochondrial disease and may be neuroprotective [22] and increase mitochondrial number [23]; however, they may also lead to abnormal mitochondrial inclusions [24]. Because of questions about long-term cardiac safety [25], the use of thiazoladendiones in mitochondrial disease patients remains questionable. Metformin can lead to lactic acidosis (MALA = Metformin-induced Lactic Acidosis) [26]), and is definitely contraindicated in mitochondrial disease. Alpha-lipoic acid should be part of a supplement cocktail if a patient has T2DM [27-29], (see also section on Supplements and Nutrition in Revised Revised Mito 101).
- 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 [30].
- 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.

Compound	Rationale
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	Inhibit complex IV, damage mitochondria
(nicotine).	
Cocaine, amphetamine, ecstacy	Increase metabolic demand on cells.

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