Summary - Exercise and Nutrition Therapy for Mitochondrial Disease
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Dr. Tarnopolsky's main areas of interest and research are mitochondrial disorders and aging. Human aging directly causes mitochondrial dysfunction, and study of older adults allows much more invasive studies, such as muscle biopsies, offering deeper understanding of the biochemistry and biology of mitochondrial dysfunction. These findings help develop countermeasures, or therapies, that might help our patients today and in the future. Dr. Tarnopolsky studies the impact of exercise on mitochondria, with and without nutritional intervention.

The spectrum of pathologic (disease-causing) disorders to physiologic adaptation is displayed on slide 3. Strength and endurance are part of adaptation. For example, high-intensity contractions (lifting weights, for example) create hypertrophy, or an increase in muscle mass, which leads to an increase in strength. Endurance exercise, with longer duration and less intense contractions, tends to cause mitochondrial biogenesis, or new mitochondria production. Understanding how the body adapts to weight training to combat weakness or increases mitochondrial biogenesis to improve mitochondrial function is clearly relevant for those who either have mitochondrial disease and muscle atrophy or a combination of both. The other side of this spectrum involves atrophy and mitochondrial dysfunction, issues that are found with muscular dystrophy and mitochondrial disease. Atrophy, which is the opposite of hypertrophy or strength, occurs when muscles become weak and leads to functional limitations. Dr. Tarnopolsky's team is working to find drugs, nutrition, and exercise therapies to improve people's functioning whether suffering from atrophy or mitochondrial disease.

Mitochondrial disease is getting a jump-start, and certainly more research dollars, as the realization that a host of other disorders have mitochondrial dysfunction as a secondary component, including obesity, type 2 diabetes, and even immobilization! For example, immobilization of a knee on a healthy, young college student for two weeks causes a reduction in mitochondrial function by almost 30%! Something as simple as breaking your ankle or having knee surgery where a cast is needed for at least six weeks can significantly impact mitochondrial function, and becomes even more important in patients with preexisting muscular dystrophy or mitochondrial dysfunction.

Nutrition -- assessing dietary soundness is vital to those with mitochondrial disease as adequate nutrition has a profound impact on healthy mitochondrial function. The study, on slide 4, entitled: "Nutritional Inadequacy in Patients with Muscular Dystrophy," was repeated in patients with Mito and the findings were just as relevant to mitochondrial disease. This study analyzed the diets of 51 adults in relation to the Canadian and US recommended dietary intake guidelines that show how many vitamins, calories, and minerals are required on a daily basis. Slides 5-7 show the percentage of patients who were not meeting the current recommendations for healthy eating.

- Energy intake is low. 68% of adults and 64% of pediatric patients were not taking in enough energy.
- Low energy intake corresponds to not getting enough vitamins, minerals, and protein. Nearly 100% of study patients did not meet vitamin guidelines. Deficiencies in some of these vitamins, for example B12, can lead to symptoms very much like the symptoms seen in Mito. Treating the deficiency is relatively easy to do and can ease symptoms significantly!
- Deficiencies may be linked to exercise intolerance or being in a wheelchair, decreasing energy expenditure and appetite as well as a lack of energy for food prep or swallowing difficulties.
- 14% of studied Mito patients were obese, which increases the risk of diabetes and impact mobility. Another 14% were underweight.

Given these findings, Dr. Tarnopolsky studied the impact of these deficiencies, retrospectively, in over 2,000 patients and discovered that many patients were deficient in key vitamins and nutrients such as Vitamins A, D, E, B12, and folate (slides 8-9).

- **Vitamin D** levels were low enough in 12% of the study group to cause rickets, weak muscles, and elevated CK levels! By new Canadian guidelines, 85% would be found deficient. These deficiencies should not be missed as these levels are easily treatable.
- **Carnitine** -- Research does not support the use of carnitine supplementation unless the patient is deficient. If low, supplementation is recommended.
- **Citrulline**, an amino acid, is often low in MELAS patients. A Japanese group believes that part of the stroke-like episodes that occur in MELAS patients is due to low citrulline and low arginine, which decreases nitrous oxides and causes vessels to spasm. MELAS patients are often supplemented with arginine and Dr. Fernando Scaglia of Texas Children's Hospital has shown that citrulline also works in the same manner (https://www.ncbi.nlm.nih.gov/pubmed/26851065).

Diet suggestions (slides 10-11):

- Undergo swallowing study, if any suggestion of dysphagia (difficulty swallowing solids or liquids).
- Take a balanced multivitamin.
- Check for deficiencies and supplement when needed.
- A deterioration of function in mitochondrial disease could be a vitamin deficiency and needs to be monitored and treated.
- Place G-tube early in kids falling off of the growth curve.
- Avoid fasting for long periods. Ten hours at night should be the maximum time of fasting because the mitochondria have to work a little harder as more fat is delivered to the mitochondria for energy.

- Consume more frequent, smaller meals.
- Patients who have a Complex I Deficiency, children with severe seizures, or people with a specific mitochondrial disease called PDH Deficiency may benefit from a high-fat diet.
- Iron supplements are recommended for low iron or ferritin levels because, when low, many of the iron sulfur clusters in the mitochondria do not operate at optimal levels. Very low levels can also lead to restless leg syndrome.
- Avoid excessive amounts of alcohol (2-3 drinks for a male and 1-2 drinks for a female). Continual or binge drinking can lead to paracrystalline inclusions, which can damage the mitochondria.
- Avoid migraine triggers: red wine, aged cheeses, etc.

Consequences of Mito Dysfunction -- Slide 12 helps to explain why the Mito cocktail is prescribed for Mito patients. Ingested food feeds into Complex I and Complex II where NADH and FADH2 also feed into the Respiratory Chain. Food, much like the wood in a fire, is slowly taken apart, or decarboxylated, and the potential energy goes into the mitochondria -- very much like pushing water up to the top of the Niagara Falls -- and then flowing through Complex V. Energy is produced. This system can only work if there is oxygen coming in and food being provided to the Complex I and Complex II. Consequences arise when this system does not work properly:

- Excessive free radicals, or reactive oxygen species, are produced that can damage lipids, proteins, DNA, and further damage the mitochondria. Part of the Mito cocktail, therefore, is to provide antioxidants to try and tone down the reactive oxygen species.
- Mitochondria provide most of the energy for cells when oxygen is present but the body has other energy sources. When the mitochondria do not work well, sugar can be utilized, although lactic acid or lactate are produced. Phosphocreatine can also be used by using the creatine stores in muscle to provide energy. Creatine is present in every cell in her body. These consequences shape how to mitigate or decrease some of the negative impact on the cells.

Mitochondrial disease strategies (slides 13-19) to improve mitochondrial function:

- Bypass the defect -- Co-Q10)3-5 mg/kg/day, has been well studied, slide 25), succinate, riboflavin
- Reduce lactate -- thiamine, dichloroacetate (rarely used today)
- Antioxidants -- Vitamin E, Alpha Lipoic Acid
- ExercisetTraining -- aerobic vs. strength
- Vasodilation -- L-arginine
- Folate deficiency -- folate, folinic acid
- Nucleotide precursors -- triacetyluridine

- Alternative energy -- **Creatine Monohydrate** improves high-intensity performance. Creatine is made in our body from amino acids. Cells make about 1 gram of creatine per day with the rest coming from the diet. People following vegan and/or vegetarian diets have very low levels of creatine. The creatine in the body is converted to creatinine.
    - Potential benefit in Mito:
        - Increase in fat-free mass
        - Increase strength and power
        - Decrease neurotoxicity
        - Antioxidant -- direct and indirect
        - Increase mitochondrial function
        - Decrease apoptosis (cell death)
        - Improved mitochondrial cell membrane potential
        - Does not cause dehydration nor liver dysfunction as some urban legends have misconstrued
        - Very few side effects

Recommended Dose: Pedi -- 0.1 gm/kg/day and Adult -- Max dose of 5 grams per day.

Dr. Tarnopolsky describes a 26-year-old triathlete who came in for a lipid study, but was found to have a mitochondrial disease (slides 20-23). The fact that this young man could competitively complete triathlons intrigued his team. A commitment to lifelong exercise compensated for his disease and allowed him to compete at high levels. Creatine and CoQ10 proved to be protective for his cells and increased his performance.

Taking supplements with food can help with absorption and may decrease stomach upset. Add one supplement at a time to better assess the effect. It is recommended you purchase a brand that has research to back up the product. For example, CoQ10 in powder form is not effective. Gels and liquids deliver the CoQ10 that is readily absorbed by the body and have been proven to improve function in Mito patients to some degree (slides 25-27). Idebenone, a CoQ10 analog, was also studied on LHON and showed very small clinical benefit and is being used infrequently at this time.

Clinical trials in Mito (slide 28-32) have had some troubles:

- Many studies were case studies, involving just two or three people.
- The patients knew whether they were on the drug or a placebo vs. using a more reliable blind study where the patient and treating staff do not know if the patient is receiving a placebo or the study drug. Dr. Tarnopolsky's study used a double-blind trial, so neither his staff nor the subjects knew what they were taking.
- Most of these supplements, and even exercise, are not patentable, therefore, big pharma companies have no interest in backing the studies. Dr. Tarnopolsky used his own personal money to fund all of his research and therapy studies for mitochondrial disease.
- Many patients were using for 5 antioxidants, which really doesn't make a lot of sense as only two are needed. Using a single agent is also not optimal.
- There are three main pathways by which mitochondria are sick:
    - Increased oxidative stress causing mitochondrial dysfunction
    - Reduction in alternative energy sources
    - Decreased ETC flux
- The best way to treat mitochondrial disease is to target these common pathways, so Dr. Tarnopolsky ran a clinical trial with the Mito cocktail focusing on supporting those three areas of dysfunction. The CoQ10 was absorbed, reflected by a five-fold increase in the blood. ATP production in white blood cells was also improved.
- The first randomized double-blind crossover study of a Mito cocktail was published in 2007. Sixteen patients remained on the cocktail for two months and then crossed over to placebo or vice versa. The cocktail included:
    - CoQ10 -- an antioxidant to bypass Complex I, mixed with vitamin E -- an antioxidant that also helps to replenish CoQ10

- Creatine -- an alternative energy source

- Alpha lipoic acid -- a mitochondrial antioxidant and it replenishes CoQ10

Results: coenzyme Q10 used was absorbed, which is important because of the old studies on the powdered form that was not absorbed.

Oxidative stress was lower, which can reduce further damage to the cells.

Lactic acid or lactate was lower, which is believed to be a reflection of less mitochondrial damage -- the lower lactic acid is, the better the mitochondrial function.

8-isoprostanes, another marker of oxidative stress, were also lower.

Exercise (slides 33-35)

Dr. Tarnopolsky's colleagues have studied high-intensity vs. endurance exercise. High-intensity exercise leads to muscle hypertrophy or growth Endurance exercise, where you do a longer duration activity, yields much more mitochondrial proliferation than weight training. The study shows an increase in strength after 3 months of exercise by 15% to 25%. This improvement in strength did not seem to cause any damage to the muscle (CK levels were monitored). The study they also showed improvement in the mitochondrial function by muscle biopsies.

Two studies were published in the same issue of *The Brain Journal* with endurance exercise, which is known to increase mitochondria. The first one was a European group that studied 20 patients with mitochondrial disease and 16 healthy controls. Participants trained for 3 months at 70% of their VO2 max four times per week, and they found a 67% increase in citrate synthase, which means about a 67% increase in total mitochondria. Their VO2 max went up 67%, which is important because many patients studied with mitochondrial disease have a maximal oxygen consumption that is almost tapped out by just doing daily activities, causing severe fatigue. Importantly, from a safety perspective, the muscle looked healthy with no increase in muscle enzyme release (CK).

Another study by Taivassalo, Gardner, Haller, and Turnbull (*Brain,* 2006) followed patients with CPEO who engaged in a 14-week training program and then deconditioning (no training) for 14 weeks (slide 37).

- Work capacity increased
- VO2 increased
- Quality of life improved and people felt better
- Mitochondrial DNA contents and mutations didn't shift
- Muscle looked very healthy
- After 14 weeks of decondition, participants lost all gains -- if you don't use it, you lose it!

- **Closing remarks**
- Think about the big picture. Exercise does not take as much time as one may think! The end goal is 20-30 minutes three to four times a week, which is just two hour out of an entire week! Get out there -- it is good for you and takes about 1% of your weekly time! Be effective with your time. Watch the news while on a stationary bike and no extra time is actually needed!
- Exercise, when added slowly and carefully, should not cause excessive fatigue and pain. Standard exercise guidelines will not work with the Mito population.
- If aerobic activity is too much at first, begin with weight training because weight training is anaerobic and does not involve the mitochondria, yet provides a bit of a spillover to help endurance. After strength is improved, carefully add in endurance activities.
- Even just two weeks of stopping exercise will bring a body back to square one. Keep moving!
- Allow day of rest for recovery.
- Exercise benefits will spill over to other body systems and improvement in overall health and quality of life.