Summary - Mito Supplement Therapy

Ted Toufas, BS, PharmD, RPh
Acton Pharmacy

Mitochondrial Background (slides 3-5)

- Each cell contains hundreds to thousands of mitochondria, depending on the type of cell. Higher energy requiring cells contain more mitochondria than lower energy requiring cells (neurons, or muscle cells vs. skin cells, for example).
- Mitochondria are energy "factories," creating ATP, the energy for the body through:
  - Krebs cycle (TCA or citric acid cycle)
  - Oxidative phosphorylation, pyruvate oxidation, and fatty acid oxidation
- Mitochondria are prokaryotic in nature (like bacteria), providing energy for the cell while the cell provides the mitochondria with the building blocks to make energy.
  - Contain own DNA (mtDNA)
  - Produce some of their own proteins
  - Self-replicate during cellular respiration, making an exact copy of itself
- Mitochondria are inherited solely from the mother/ovum (egg). This statement has been challenged recently, but no proof exists that sperm contribute mtDNA to fetal cells. If a mother has mitochondrial disease, it will be passed down to her children and may be amplified over time. Some mitochondrial DNA mutations or damage also comes from nuclear DNA, inherited by one (mother or father) or both parents.
- Mitochondria may be damaged and produce disease through spontaneous mutations. These individuals would have parents with normal, healthy mitochondria.
- **Cell Structure -** Simplified cell with three mitochondria is depicted. Cells actually have many more mitochondria, but the image provides a good visual of cell structure.
- **Damage to mitochondria *cannot be reversed!***
  - Unhealthy mitochondria continue to reproduce, replicating (copying) the damage. Eventually, each cell becomes more and more populated with damaged, ineffective, or non-functioning mitochondria. The **threshold effect** describes the point when the tissue cells have enough damaged mitochondria negatively impacting energy production to cause tissues to show signs of failure.
  - Everyone has progressive damage to their mitochondria, which is the cause of aging. The damage is more pronounced in those unable to physiologically cope with the damage.

Krebs Cycle (Citric Acid Cycle) (slide 6)

- Key component of energy production, occurring in the mitochondria.
- Acetyl-CoA has a critical role in making ATP (energy).
- Pyruvic acid is supplied to mitochondria by the cell.

Electron Transport Chain (ETC) (slides 7-8)

- Proton (H+ or Hydrogen ion) gradient is created in the intermembrane space and flows into the matrix thorough ATP synthesis.
- Complex I - NADH/Co-Q reductase
- Complex II - Succinate/Co-Q reductase
- Complex III - Co-Q/Cytochrome bc1 reductase

- Complex IV - Crytchrome c oxidase
- Complex V - ATP Synthase - Processes proton gradient and creates ATP
- A deficiency in one complex clogs up the next step, like a dam, only allowing restricted water flow downstream (slide 8).
- Note that Co-Q10 is a key component of many of the complexes and, therefore, a main part of supplementation.
- Reductase and oxidation are the two biggest and opposite reactions in energy production, also playing a role in supplementation.
- The three stars on slide 8 show critical sites of **reactive oxygen species,**which is basically a free radical production, lending to cell and mitochondria damage. The free radicals need to be reduced to harmless water in all by utilization of different enzymes. When the enzymes are compromised, the free radicals are not quenched (donating electrons to render free radicals harmless). The unquenched free radical may then bind to proteins, lipids or DAN, changing their structure and making them non-functional (slide 9). Free radical damage could lead to mitochondrial disease or mitochondrial dysfunction. Highly energy dependent tissues (brain, kidney, skeletal muscles, heart, liver) are most vulnerable to this damage (slide 10), explaining why more mitochondrial diseases are neurodegenerative and neuromuscular.

Supplementation (slide 13)

- Vitamins, co-factors, and antioxidants are the first line of supplementation.
- Formulas vary from patient to patient based on specific metabolic needs (blood work, muscle or tissue biopsy, and/or DNA testing), even within the same genetic mutation. Individuals have unique biochemical constitutions, and, accordingly, should have unique supplementation plans.
- May need increased dose or extra supplementation during acute exacerbations or mitochondrial disease, stress, or infection.
- Doses may start out the same for all patients initially, depending on provider, and then be adjusted as lab values and patient's response to therapy are reassessed. Keep in mind that each individual patient will have a unique response to treatment.
- Most data on supplementation is anecdotal, without much clinical evidence to support a positive response to the Mito Cocktail. Dr. Parikh, et.al published "A Modern Approach to the Treatment of Mitochondrial Disease," the most current reference for supplementation, implementation, and dosing. (http://www.ncbi.nlm.nih.gov/pubmed/19891905) (slide 14)

Coenzyme Q-10 (Co Q-10) (slides 15-16)

- Created in all mammalian mitochondria.
- Vital part of the ECT - transfer of electrons from Complex I and II.
- Found in all cell and organelle membranes, participating in reduction/oxidation reactions in the body, helping to quench free radicles.
- Involved in other functions in the body such as programmed cell death (apoptosis), permeability of mitochondrial pores, and as a cellular signal by activating uncoupling proteins.
- Kinetics - fairly insoluble in water, powder formulations have poor absorption, with improved bioavailability when use nano-particles in suspension.

- FDA approved for treatment of mitochondrial disease.
- Have medical professional guide dosing, especially at higher doses.
- Three types of Co-Q-10
- **Ubiquinone**
  - Most common and has been available the longest
  - Oxidized from of Co Q-10
  - Potency may vary greatly between manufacturers
  - Half life of 33 hours
- **Ubiquinol**
  - More recent
  - Reduced form of Co Q-10
  - Absorbed 3-5 times more effectively
  - Half life of 48 hours
- **Idebenone**
  - Synthetic form, which is not naturally found in the body
  - Possible stimulation of nerve growth factor, serotonin, and dopamine
  - May be beneficial to Alzheimer's, Parkinson's, and Huntington's diseases, as well as Friedrich's Ataxia
  - May see a better response in Mito patients with significant neurological symptoms
  - Body can convert ubiquinone to ubiquinone and vice versa when needed.
  - Excess amounts are stored in fat cells and can become harmful.
  - Common side effect of wakefulness, so take last daily dose in afternoon.

Riboflavin (Vitamin B2) (slide 17)

- Water soluble - excreted in urine.
- Serves as flavoprotein precursor. Flavoproteins remove free radicals from the body and helps apoptosis.
- Utilized by many proteins in the body.
- Key building block for Complex I and II, as well as a cofactor in several other enzymatic reactions involving Fatty Acid Oxidation and the Krebs Cycle.
- Multiple Acyl-CoA Dehydrogenase Deficiency (MADD), an inborn error of metabolism, is caused by a gene mutation. Riboflavin supplementation alleviates symptoms and slows disease progression.
- High doses can cause anorexia (lack of appetite), nausea, and change in urine color to bright orange.

Creatine Monohydrate (slide 18)

- Present in all cells, either from diet or made within the body.
- Some have difficulty producing creatine and absorbing it from the diet.
- With anaerobic crises, when oxygen is not available to produce energy, creatine acts as an energy storage reservoir, storing excess phosphate molecules. In times of need, the phosphorus comes off the creatine and is used to make energy. Specifically, creatine undergoes a reaction with ATP to phosphocreatine in the mitochondria, creating a source of energy for anaerobic exercise (muscles work without oxygen). This solution for energy crises is a short term fix, but can

help to build muscle mass and offer more times that the muscle can contract, which is why creatine is used by many elite athletes.
- Found in tissues with high energy demands, yet is reduced in muscle tissues of patients who have mitochondrial myopathies.
- Small studies on creatine supplementation have shown an increase in high intensity, isometric, anaerobic and aerobic power, but no effect on body composition, 2-minute walk test, or activities of daily living scores (ADLs).

Levocarnitine (L-Carnitine, Carnitine) (slides 19-20)
- Critical in the conversion of fatty acids to energy, by-passing many steps needed to convert glucose to energy and jumping right into the Krebs cycle.
- May help prevent CoA depletion and removal excess acyl compounds, which could be toxic.
- Some is endogenously produced, but the majority come from the diet.
- Side effects - body, urine, and fecal odor changes (fishy smell) due to the ammonia like composition.

Folinic Acid (Leucovorin) (slide 21)
- Reduced form of Folic Acid (Vitamin B9).
- Co-factor in multiple metabolic reactions.
- Some case reports state that mitochondrial disease may lead to cerebral folate deficiency.
- Deficiency primarily seen in Kearns-Sayre Syndrome.
- Side effect can be itchiness.

N-Acetylcysteine (NAC) (slides 22-25)
- Modified cysteine molecule, which is a part of **glutathione,** thebody's natural, very powerful antioxidant**.**
- Inhaled for cystic fibrosis to loosen mucous in lungs.
- Injected for acetaminophen overdoses (Tylenol).
- Supplement for kidney disease to help damaged tissue.
- In mitochondrial/metabolic therapy, used for energy dependent tissues as a/an:
  -- antioxidant.

  -- replenishing agent for glutathione by reducing glutathione back to its reduced state and keeping it more active within the body. Glutathione becomes oxidized when it scavenges damaging free radicals, rendering it non-functional. NAC returns it to a healthy, functional state.

- Difficult to replace glutathione as body digests oral dose into amino acids, destroying the molecule. Topical administration does get the molecule into the body, but is expensive, not covered by most insurances, and is hard to keep a constant and consistent supply available to the body. IV administration is ideal as it distributes well to the body and is a constant administration. This method, however, is expensive and cumbersome to patients.
- NAC is cheaper and can be taken orally as a powder or capsules. Liquid formulations are unstable, except injectable forms, which are sealed, under

pressure, and contain preservatives. Strong sulfur odor/taste (rotten eggs) hinders administration to children. Most patients prefer capsules.
- NAC that is not utilized in the body will remain for a while, waiting to be used by glutathione or as an antioxidant on its own. After a while, it is eliminated by the body, rendering higher doses safe and well tolerated.

Other Vitamins and Redox Agents (slides 26 - 27)
- **Thiamine (Vitamin B1)** - critical in carbohydrate metabolism and indirectly in nucleic acid (DNA base) synthesis.
- **Ascorbic Acid (Vitamin C)** – water-soluble antioxidant that helps replenish Vitamin E.
- **Tocopheryl (Vitamin E)** – lipid- (fat) soluble antioxidant in cellular and organelle membranes.
- **Alpha-Lipoic Acid** - powerful antioxidant for cell and mitochondria.
- **Pyridoxine (Vitamin B6)** - component of neurotransmitter synthesis/development, which helps with neuropathy and nerve pain.
- **Niacin (Vitamin B3)** - deficiency leads to slower metabolism and an intolerance to cold.
- **Cyanocobalamin (Vitamin B12)** - vital to red blood cell growth and proliferation as well as DNA synthesis and utilization in the body.
- General dose ranges for mitochondrial disease (slide 27) tend to be higher than RDA (recommended daily allowance), which are based on healthy people, without metabolic issues. Please consult a qualified physician to optimize dosing and keep side effects to a minimum. Some prescribers begin one supplement at a time and wait to see results, while other prescribers compound or begin many supplements together right from the start. The key is to maintain good, ongoing communication with the provider.

Side Effects/Toxicity/Monitoring (slide 28-29)
- All vitamins cause GI upset due to the fact that the dissolving a massive amount of concentrated nutrients, causes the GI tract to floods with water.
- Leads to nausea, diarrhea, and gas - to mitigate:
- Take with food and water.
- Begin with ¼ to ½ of the daily dose for the first week, then increase over the next couple of weeks until reach full dose.
- Allow time for the body to adjust - do not get discouraged and stop the medication.
- Speak with the prescriber or pharmacist for help to strategize to minimize side effects.
- Overall, these medications are safe, and even if given to wrong child or in overdose, only will result in GI distress.
- Chronic use of certain vitamins/supplements may lead to toxicity.
  - CoQ-10 - possible pro-oxidant effects and pro-signaling pathways triggered which can lead to harm. Too much stored Co Q-10 can create free radicals instead of quench them!

- Creatine - May elevate serum creatine and crystallize in kidney, which is especially problematic with renal impairment.
- Levocarnitine - possible buildup of toxic metabolites in renal impairment and possible cardiac rhythm disturbances.
- B Complex -neuropathies.
- Vitamin E - possible adverse cardiac risks if taking more than 400 IU/day over an extended period of time.
- Drug interactions are mild to non-existent.
  - Possible erythromycin, warfarin interactions, rendering them more or less effective respectively.
  - Space from osmotic laxatives (PEG 3350) and bulk forming laxative by 1 hour prior or 2 hours after to maximize absorption.
  - Space appropriately from Cholestyramine (cholesterol binder).

Diet, Lifestyle and Nutrition (slide 30)

- **Avoiding Mitochondrial Toxins**- Certain medications may exacerbate Mito symptoms or are directly toxic to mitochondria. Speak with doctor or pharmacist about possible Mito toxic medication and to assess the risk to benefit ratio for individual medications.
  - Certain antibiotics - can cause issues because mitochondria are like little bacteria (Cipro, a fluoroquinolone, for example).
  - Valporic Acid - inhibits FA oxidation, Krebs Cycle and ECT; carnitine depletion.
  - Anti-retrovirals (HIV meds, primarily) - impairment of mtDNA replication; lactic acidosis; carnitine depletion; lipodystrophy.
  - Statins - Co Q-10 depletion.
  - ASA (aspirin) - inhibition and uncoupling of ETC.
  - Aminoglycosides (antibiotic), platinum chemo agents - impaired mtDNA translation.
  - APAP - oxidative stress (creates reactive oxygen species (ROS) compound called NAPQI).
  - Metformin - inhibition of ETC; enhanced glycolysis.
  - Beta-blockers - oxidative stress.
  - Steroids - unknown.
- http://www.mitoaction.org/blog/mitochondrial-disease-and-toxins
- http://www.mitoaction.org/blog/medication-exposures-mitochondrial-toxicity

Therapy Expectations (slide 31)

- Not something that will work overnight! Allow 1-2 months of therapy before making an assessment about therapeutic value.
- Follow up with prescriber for additional blood work or testing.
- Keep a diary, beginning 1-2 weeks before therapy, tracking how feel, fatigue, pain, symptoms, thought process, behavior, sleep, etc. Track morning, noon, and night, if possible. Review every few weeks to a month to see trends. MitoAction tracker app: http://www.mitoaction.org/mitoaction-app.
- If decision made that meds are not worth the cost, stop the med, but continue the diary. Restarting the med is an option if feeling worse without the med.

Formulations and Safety (slides 32-38)

- Many ways to make compounds:
  - Suspensions, powders, capsules, effervescent packets, and gummies.
- Depending on dose of supplements per day, some formulation are preferred over others due to the high volume of supplements.
  - Capsules - 2-10 capsules per day, help with taste.
  - Powder - a calibrated scoop twice a day, help with taste, can be flavored
  - Suspension - 5-10 ml twice a day, good for absorption disorders, taste aversion, can add flavors or sweetening.
  - Gummies - harder to formulate since only a maximum of 300 mg of medication can be added to 1 gummy. Typical formulation require up to 30 gummies a day to meet daily dose!
  - Effervescent packets - may take up to 5 packets per day, but taste better than other formulations due to the fizzing keeping drug off of the taste buds.
- All formulations should use divided dosing - at least twice a day administration and up to four times a day.
  - Provides a more constant level of the supplements in the body.
  - Leads to better GI absorption because not flooding GI track.
  - Decrease risk of GI upset.
  - Help those with absorption issues.
  - But, decreases compliance because of the need to remember to take multiple doses and trying to get child to take bad tasting medication more often or during school hours can be difficult.
- Safety - Check where supplements are coming from!
  - If buying over the counter (OTC) supplements, avoid non-pharmacy stores where the source of supplements is not regulated. Issues with purity and contamination have occurred.
  - Use brand name supplements like: Metagenics, Epic4Health, Solgar, Rainbow Light, Pure Encapsulation etc. Brand name products have a track record of safety and quality because the products are tested.
  - NO over the counter supplement is regulated by the FDA, meaning they do not undergo testing and do not have to have what is claimed on the bottle. If you buy CoQ-10 600mg capsules, the capsules may have more or less of the medication than stated.
  - Call the company and ask about quality control!
  - Compounding Pharmacies source medications from FDA approved wholesalers who are required to maintain a certain degree of testing and standards. If a sample analysis fails, the drug is rejected.
  - Compounds are NOT FDA approved, but ingredients should be sourced from FDA approved facilities.
  - Speak with pharmacist about quality standards and who is their source.
  - If they are PCAB (Pharmacy Compounding Accreditation Board) Certified, they are required to follow good compounding practices.
  - Some FDA wholesalers are located outside the country, but are still held to high standards of quality control. At times, other counties are the only source for certain medication or ingredients.

- Cost - using trusted sources for OTC medications may be more expensive, but is worth the peace of mind knowing that the quality is high.
  - Compounding is even more expensive as there is more rigorous testing procedures utilized at both the wholesaler and pharmacy level to make the medication.
  - Pharmacies work with insurance companies to cover medications, though more and more insurance companies are requiring prior authorizations (PAs) for compounds or not covering the medications. PAs are additional paperwork filled out by the doctor or pharmacist, faxed to the insurance company, reviewed the insurance company, with a decision made to cover or deny the medication. PA processing can take 2 days to 2 months.