Summary - Mitochondria and MitoQ: A Research Update

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Today's discussion will cover the history of this company, the research happening over the last year, explain what MitoQ is and how it works, and review some of the recent research on this product. As a disclaimer, topics discussed today have not been evaluated by the FDA and MitoQ is not intended to diagnose, treat, cure, or prevent any disease.

The History of MitoQ

The concept of targeting the mitochondria with antioxidants was developed by researchers at Otago University in Dunedin, New Zealand, at the turn of the century (slide 7). These researchers studied the link between oxidative stress, mitochondrial dysfunction, and disease, theorizing that taking high doses of antioxidants should decrease disease. Early studies, however, showed that the bigger the clinical trial, the worse the antioxidants preformed. Researchers then thought to target the mitochondria specifically by getting the antioxidants to the source of oxidative stress. Knowing the mitochondria have a negative charge, by adding a positive charge to the antioxidants, researchers found a way to get the antioxidants into the mitochondria in meaningful levels, as the opposite charges attract each other. MitoQ was formed at that time. Early studies on Parkinson's disease (PD) did not give hopeful results, but subsequent mouse model studies on PD do demonstrate that if MitoQ is given early enough in the disease, onset and progression of the disease are delayed. In PD, about 80% of the damage is done by the time symptoms are displayed, which would explain why MitoQ's first study failed. Unfortunately, this study failure caused funding to leave MitoQ, despite positive results in a Hepatitis C study. The company went silent for a few years around 2007, but researchers continued to work and strengthened findings to support the link between mitochondrial dysfunction and disease. Researchers then began requesting MitoQ for use in research with animal models with various diseases involving mitochondrial dysfunction. This research continued to demonstrate that MitoQ had quite significant beneficial effects in many different diseases involving mitochondrial dysfunction. MitoQ was also determined to be a perfectly safe compound, and the company pivoted and launched skincare products and supplement range products. After the launch of the supplements, MitoQ was given to mice in a research trial for multiple sclerosis (MS). MitoQ got these mice up and running again. The MS community then became quite engaged with MitoQ, finding that MitoQ helps with the fatigue and general symptoms associated with MS (slide 8). MitoQ was then involved in a study at the University of Colorado regarding dysfunction of arteries. With aging, arteries become stiffer and less able to dilate when necessary, but after 4 weeks of MitoQ therapy, arteries functioned like a juvenile (slide 9). In the last 4 years, MitoQ has over 200,000 patient months' experience with MitoQ in over 100 countries (slide 10) with increasing growth each year.

Mission Statement
MitoQ's mission is to raise awareness of mitochondria and the link between optimal mitochondrial function and longevity (slide 11). Mitochondria are directly tied to health and 20% of body weight is made up of mitochondria. Mitochondria are vital to life. All experience some degree of mitochondrial dysfunction, especially as aging occurs. By age 40, Mito dysfunction is rising, although symptoms may not be evident. By the fifth and sixth decades, however, the mitochondria are in enough decline that a decrease in energy as well as other symptoms become pronounced. For those born with some sort of mitochondrial dysfunction, symptom presentation and progression are typically accelerated. MitoQ aims to help alleviate or slow this process of mitochondrial dysfunction.

What is MitoQ?
MitoQ is a derivative of Co-enzyme Q10, which is a very important antioxidant inside the mitochondria (slide 12). CoQ10 is a very long, oily molecule that has two functions:

- Involved with the generation of ATP in the mitochondria
- Powerful antioxidant

This large molecule does not cross the mitochondrial membrane easily, therefore mitochondria make their own CoQ10 within the cells. Of note is that much of the CoQ10 supplements do get into the bloodstream, but do not make it into the cells in any significant quantities. MitoQ is a shortened CoQ10 derivative with an added positive charge (slides 13-14), which helps it pass into the negatively charged mitochondrial. In fact, MitoQ gets into the mitochondria roughly 800 to 1,200 times more than regular CoQ10. Until now, no one has been able to get antioxidants back into the mitochondria.

- Mitochondria generate energy for cells and in the process generate 90-95% of the free radicals in our cells.
- Because of the production of free radicals, mitochondria are teeming with antioxidants, especially when healthy and young. Those antioxidants protect the mitochondria from the free radicals that have been generated during the energy production process.
- When antioxidant capacity declines in the mitochondria, a cell ages, which occurs in certain diseases in which the mitochondria do not work well. Compare the cell to a car engine. A new engine runs clean, but an older engine produces more pollution and runs rough.
    - Mitochondria are damaged due to exposure to oxidative stress.
    - Mitochondria leak free radicals into the cell and cause the cell to be under stress, damaging the DNA and cellular machinery.
- By increasing levels of antioxidants within the cells, the cells are essentially protected from this process of aging or disease.

MitoQ goes rapidly from the stomach to the bloodstream and into the cell. It protects the mitochondrial membrane. The inner mitochondrial membrane is responsible for many processes (see slide 15 for detailed list). MitoQ helps to stabilize and protect that

membrane, enhancing all the activities of the membrane and the mitochondria, including production of ATP. MitoQ is believed to be so successful because of its impact on all listed processes, not just one cellular function.

What Makes MitoQ Different from Other Antioxidants?

1. Mitochondria-targeted antioxidant -- protecting the mitochondria from oxidative stress by putting a ring of protection around the mitochondria.
2. Selective vs. broad spectrum -- not all free radicals are bad. Too few free radicals are not good for the cell, just as too many are harmful. The mitochondria use free radicals to communicate messages between the cell, the mitochondria, and the nucleus. Shutting down the signaling is not good for the cell. A recent study demonstrated that those taking large amounts of specific antioxidants have a higher chance of death over the long term than those not taking antioxidants. Another study looked at two groups of older men, one taking antioxidants and the other not, who were exercising. Both groups had benefit in terms of increased fitness, but the group taking high doses of antioxidants had much less muscle growth, which is believed to be from the loss of free radical signaling within the cell. MitoQ helps the cell stay in balance in terms of free radicals.
3. Recycling antioxidant (slide 16) -- MitoQ delivers back some natural antioxidant, which is designed to quench some free radicals while ignoring others, thus leaving the messaging system intact. MitoQ sits within the mitochondrial membrane and as it quenches a free radical, MitoQ recycles and is ready to quench another free radical. Not much MitoQ, therefore, is needed to benefit the cells the daily recommended dose is 5-10 mg as compared to much higher doses of CoQ10.

Why is this Important?

Mitochondrial dysfunction is at the root of over 200 diseases and conditions, including Parkinson's, Alzheimer's, obesity, epilepsy, cancer, diabetes, MS, rheumatoid arthritis, aging, heart disease, and hepatitis (slides 17-18). There many reasons to keep a body's mitochondria tuned up and healthy, especially for the organ systems rich in mitochondria. Mitochondrial function declines about 10% per decade after the age of 30, so all are impacted by some degree of mitochondrial dysfunction as we age.

MitoQ Research (slides 20-26)

- $500 million spent on research
- Over 200 published papers
- Over 70 disease models involved in research
- NIA (National Institute of Aging) funded programs -- only products that are believed to improve lifespan by at least 10-15% are asked to join this program
- Clinical trials -- many groups are asking to use MitoQ in their disease-specific trials as well

Mitochondrial Research is just beginning. Science knows quite a bit about a small area of mitochondrial health and disease, with so much yet to learn. Research is rapidly adding to the knowledge base. Because MitoQ works to promote healthy mitochondrial membranes, a wide sector of mitochondrial health is positively impacted, including cell

death and survival, oxidative phosphorylation, calcium homeostasis, and ROS signaling.

The website https://mitochondrialdiseasenews.com/ lists recent study results, including (slides 26-33):

- Mitochondrial Control renewal of the Intestinal Wall, Development of Gut Diseases
- Average Mitochondrial Function May Increase Risk of Diet Induced Fatty Liver Disease
- Mitochondria Transplants Ease Hypoxia-induced Pulmonary Hypertension in animal study
- Studies Indicate Mitochondrial Mutations are the Cause of Autism
- Mothers Can Pass Obesity to Offspring through Mitochondrial DNA in Eggs, study finds
- Mitochondrial Changes Help Immune Cells React to Bacteria
- Mitochondrial Matchmaking -- New England Journal of Medical -- mouse models bred to have mitochondrial disease are studied. These mice have a shortened lifespan, weight gain from high-fat diet, increased ROS production, decreased ATP, and decreased rate of respiration (ox-phos), which is reversed with transplant of healthy mitochondria.
- Reversing Aging: Cellular Damage could be Reversed by Activating Genes in Mitochondria
- Targeted Transplantation of Mitochondria to Hepatocytes
- Researcher Remove Mutation DNA from Mitochondria to Slow or Reverse a Cause of Aging

Human Research (slides 39-44)
Mendus Trial -- Looked at impact of MitoQ on Fibromyalgia (FM) and Chronic Fatigue Syndrome (CFS) in a 12-week, 3-arm-blinded, crossover trial.

- FM arm -- 24-33% reduction in pain, 10-13% improvement in cognitive function
- CFS blinded arm -- no significant benefit and need to evaluate why
- CFS open arm -- increase in energy (26% and 32%), sleep quality (17% and 35%), mental clarity (18% and 51%), verbal reasoning (19% and 30%), as well as a modest reduction in pain at 6 weeks (13%)

Spanish Trial -- MitoQ modulates oxidative stress, inflammation. and leukocyte-endothelium interactions in leukocytes isolated from type 2 diabetic patients (Escribano-Lopez, et.al. 2016

- 169 subjects: 98 with Type-2 diabetes (T2D) and 71 control subjects
- Study aim -- examine reduction of oxidative stress and metabolic parameters and leukocyte-endothelium interactions
- Leukocytes from T2D patients showed increased ROS (free radical) production, but MitoQ treatment brought these values down to the levels of controls. MitoQ increased glutathione peroxidase (ROS neutralizing enzyme) levels in both patients and controls.

- MitoQ treatment significantly reduced the adhesion of leukocytes to endothelial cells in the T2D group.
- MitoQ significantly reduced levels of NFKB-P65 and TNF group.
- "Overall, our findings provide a better understanding of the pathophysiological mechanisms occurring in the leukocytes/endothelium of T2D patients. They suggest that increased inflammation and oxidative stress, together with the NFKB-P65 activation and increased pro-inflammatory cytokine TNFa, contribute to the enhanced interaction between these cells, which augments the risk of CVD. Importantly, treatment with potential beneficial effects for preventing cardiovascular diseases in T2D."

Colorado Trial -- Novel antioxidant makes old arteries seem young again by restoring endothelial function in old mice taking MitoQ (University of Colorado study).

Delaware Trial -- Mitochondrial Oxidative Stress and Vascular Health in Chronic Kidney Disease

Planned Human Research
- Diabetes
- Multiple sclerosis -- University of Oregon
- Asthma

Mouse Model Research (slides 45-50)
Mitochondria-targeted antioxidant MitoQ attenuates liver fibrosis in mice
- Oxidative stress plays an essential role in liver fibrosis. This study investigated whether MitoQ, an orally active mitochondrial antioxidant, decreases liver fibrosis. Data indicates that mitochondrial-reactive oxygen species play an important role in liver fibrosis and that mitochondria-targeted antioxidants are promising potential therapies for prevention and treatment of liver fibrosis.
- A mitochondrial-targeted ubiquinone modulates muscle lipid profile and improves mitochondrial respiration in obesogenic diet-fed rats
- The prevalence of the metabolic syndrome components, including abdominal obesity, dyslipidemia, and insulin-resistance, is increasing in both developed and developing countries. It is generally accepted that the development of these features is preceded by, or accompanied with, impaired mitochondrial function. For this purpose, 24 young male Sprague-Dawley rats were divided into three groups and fed one of the following diets: (1) control, (2) high fat (HF) and (3) HF+MitoQ. After 8 weeks, mitochondrial function markers and lipid metabolism/profile modifications in skeletal muscle were measured. The HF diet was effective at inducing the major features of the metabolic syndrome -- namely, obesity, hepatic enlargement, and glucose intolerance. MitoQ intake prevented the increase in rat body weight, attenuated the increase in adipose tissue and liver weights, and partially reversed glucose intolerance. These lipid modifications were accompanied with a decrease in mitochondrial respiration. MitoQ intake corrected the lipid alterations and

restored mitochondrial respiration. These results indicate that MitoQ protected obesogenic diet-fed rats from some features of the metabolic syndrome through its effects on muscle lipid metabolism and mitochondrial activity. These findings suggest that MitoQ is a promising candidate for future human trials in the metabolic syndrome prevention.

- Selective Mitochondrial Targeting Exert Anxiolytic Effects in Vivo
- Current treatment strategies for anxiety disorders are predominantly symptom-based. However, a third of anxiety patients remain unresponsive to anxiolytics highlighting the need for more effective, mechanism-based therapeutic approaches. Comparison of high- vs. low-anxiety mice identified changes in mitochondrial pathways, including oxidative phosphorylation and oxidative stress. In this work, selective pharmacological targeting of these mitochondrial pathways exerts anxiolytic effects in vivo. High-anxiety-related behavior (HAB) mice were treated with MitoQ, an antioxidant that selectively targets mitochondria, resulting in decreased anxiety-related behavior in HAB mice. This anxiolytic effect was specific for high anxiety as MitoQ treatment did not affect the anxiety phenotype of C57BL/6N and DBA/2J mouse strains. Studying molecular underpinnings of the MitoQ-driven anxiolytic effect found that MitoQ treatment alters the brain metabolome and that the response to MitoQ treatment is characterized by distinct molecular signatures. These results indicate that a mechanism-driven approach based on selective mitochondrial targeting has the potential to attenuate the high-anxiety phenotype in vivo, thus paving the way for translational implementation as long-term MitoQ administration is well tolerated with no reported side effects in mice and humans. In short, MitoQ helped relieve anxiety in this study.

MitoQ supplementation improves motor function and muscle mitochondrial health in old male mice -- Colorado University

The mechanisms underlying the development of motor dysfunction with aging are incompletely understood, but a compelling hypothesis is that age-related increases in mitochondria-derived reactive oxygen species (mtROS) may contribute. Motor function was assessed using a battery of tests in young (4 months) and old (26 months) mice at baseline and after 4 weeks of MitoQ or vehicle (n=20/group). MitoQ improved mass normalized grip-strength (+23.1%) and completely restored endurance rota-rod-run time (+95.2%) and distance (+69.1%) in old animals supplemented with MitoQ but not old control or young male mice.

Experimental MitoQ treatment fails Prevention of Age-Related Muscle Mass, Function Loss in Mice

- More work is needed in this area, but this study failed to show that MitoQ prevented muscle loss and function in older mice.

Anti-Aging Research (slides 51-54)
Interventions Testing Program -- for longevity intervention proposals. Studies and results will be forthcoming. MitoQ is excited to be included in this program.

MitoQ counteracts telomere shortening and elongates lifespan of fibroblasts under mild oxidative stress

- Minimizing oxidative stress significantly slows down telomere shortening and prolongs replicative lifespan. Moreover, accelerated telomere shortening in response to increased mitochondrial ROS production induces premature senescence-like arrest under conditions of mild stress such as chronic hyperoxia. Intense, acute stress, which leads to an immediate arrest in the vast majority of cells, is of course telomere length-independent (Chen *et al*., 2001; Gorbunova *et al*., 2002).

Meta-Analysis -- Review of over 200 papers, measuring of 220 significant endpoints.
Increased:

- Cell Survival
- Mitochondrial Membrane Potential
- Mitochondrial Respiratory Rate
- ECT activity
- ATP
- GSH
- Cardiolipin
- AMPK
- Anti-inflammatory IL
- PGC-1a

Decreased:

- Caspase-3 activity
- Protein-carbonyl formation
- Lipid peroxidation
- ALT
- Heart rate
- Apidosity
- AST
- TNF-a
- NFk8
- Inflammatory IL

Additional Reading

Novel antioxidant makes old arteries seem young again, CU-Boulder study finds
Antioxidant reverses multiple sclerosis-like disease in mice
Mitochondrial Disease News
The influence of MitoQ on symptoms and cognition in fibromyalgia, myalgic encephalomyelitis and chronic fatigue
The mitochondria-targeted antioxidant MitoQ modulates oxidative stress, inflammation and leukocyte-endothelium interactions in leukocytes isolated from type 2 diabetic patients
Mitochondrial Oxidative Stress and Vascular Health in Chronic Kidney Disease

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