Mitochondria: Overlooking These Small Organelles Can Have Huge Clinical Consequences in Treating Virtually Every Disease

by Chris D. Meletis, ND, and Kimberly Wilkes

The mitochondria are tiny organelles that are often overlooked in the treatment of disease. Yet, mitochondrial dysfunction drives the development of – or worsens the symptoms of – some of the most devastating diseases of modern times, including cancer, cardiovascular disease, Alzheimer's, Parkinson's, autism, and diabetes, as well as many other conditions that don't at first glance seem related to the mitochondria such as autism, bipolar disorder, or osteoarthritis. Ironically, not only are the mitochondria often ignored by many conventional doctors in the treatment of disease, the same patients suffering from mitochondrial-related diseases are given drugs that impair mitochondrial function.

The volumes of research about the mitochondria and mitochondrial dysfunction indicate that what is now known about the mitochondria extends far beyond what we learned in basic biology. An abundance of fascinating research continues to spotlight the role that mitochondrial dysfunction plays in most – if not all – diseases. Mitochondrial dysfunction's role in disease is particularly concerning, given that the mitochondria of the modern human are subjected to some assaults never experienced by people who lived before the early 1900s. Therefore, it's critical to become familiar with these tiny organelles, to learn how their dysfunction can contribute to disease, and to discover the best ways to protect the mitochondria and ensure that they are functioning optimally.

How Mitochondria Function: A Brief Recap

Before we discuss mitochondrial dysfunction, it is important to review the way in which mitochondria function. It starts with glycolysis, which occurs outside the mitochondria. Glycolysis converts glucose into pyruvate, which is then converted into acetyl-CoA. The citric acid cycle (also known as the Krebs cycle) then takes over inside the mitochondria to convert the acetyl-CoA into the reduced form of nicotinamide adenine dinucleotide (NADH) and the reduced form of flavin adenine dinucleotide (FADH2), which are important in a process known as oxidative phosphorylation (OXPHOS).

Through their oxidation and breakdown, NADH and FADH2 help fuel OXPHOS, which is responsible for producing the energy that powers cells. In OXPHOS, electron donors transfer electrons to electron acceptors by using electron transport chains. Energy is released when an electron is transferred to an acceptor such as oxygen. The mitochondria, using the enzyme ATP synthase, use the energy produced in the electron transport chain to manufacture adenosine triphosphate (ATP) from adenosine diphosphate (ADP). ATP is to our bodies what gasoline is to our cars. We could not function without it and any defects in ATP production often result in fatigue. Metabolic processes that use ATP as an energy source convert it back into its precursors. Therefore, ATP is continually recycled.

The energy produced by OXPHOS causes protons (particles with positive electric charge) to be transported across the inner mitochondrial membrane. This creates a gradient that produces additional energy.

There are five complexes in the electron transport chain:

- Complex I (NADH dehydrogenase) – Complex I is an enzyme that catalyzes the two-electron oxidation of the reduced form of nicotinamide adenine dinucleotide (NADH) by coenzyme Q10 (ubiquinone). During Complex I, ubiquinone also is reduced to ubiquinol, which results in the generation of energy by the creation of a proton gradient.
- During Complex II (succinate dehydrogenase) reactions, succinate is oxidized into fumarate and ubiquinone is reduced. This process does not produce as much energy as Complex I, and is unable to create a proton gradient.
- Complex III (cytochrome c reductase) results in the oxidation of one molecule of ubiquinol and the reduction of two molecules of cytochrome c, a protein responsible for transferring electrons. This reaction very efficiently transfers protons across the mitochondrial membrane, creating a proton gradient, thereby assisting with energy production.
- Complex IV (cytochrome c oxidase) is an enzyme that oversees the last step in the electron transport chain. During this reaction, electrons are transported to oxygen, which is reduced to water, and protons are transported across the mitochondrial membrane.

- Complex V (ATP synthase) is the last enzyme utilized in oxidative phosphorylation. By tapping into the energy reservoir generated by the proton gradient across a membrane, ATP synthase assists with the creation of ATP from ADP and phosphate.

Oxidative phosphorylation is the most efficient ATP producer. For example, for every 1 glucose molecule oxidized, only 2 ATP molecules are generated by glycolysis, whereas the electron transport chain can generate between 30 to 36 ATP molecules.

Oxidative phosphorylation is a critical part of normal metabolism, but it has a dark side as well. The process produces reactive oxygen species (ROS) – for example, superoxide and hydrogen peroxide – which can result in cellular damage and lead to disease and accelerated aging.[1]

Are GM Foods Harming the Mitochondria?

The mitochondria are subjected to a number of modern-day insults, including toxins. Although there are many toxins that impair mitochondrial function, one of the most prevalent is glyphosate (used in Roundup). Because genetically modified (GM) foods are engineered to be resistant to glyphosate, they're slathered with this herbicide.

This is particularly disturbing given that every year, Americans are eating their body weight in GM foods, according to an analysis by the Environmental Working Group.[2] Additionally, near the Mississippi Delta farmlands, glyphosate and its degradation product aminomethylphosphonic acid (AMPA) were found in 75% or more of air and rain samples in 2007.[3] This indicates that glyphosate is extremely prevalent in agricultural areas.

Glyphosate is especially toxic to the mitochondria when it is combined with surfactants or adjuvants, primarily in the formulation known commercially as Roundup. These surfactants or adjuvants are claimed to be inert, but research paints a different picture. Researchers have shown that adjuvants in glyphosate-based herbicides were as much as 10 times more harmful than glyphosate itself.[4] One group of researchers found Roundup to be 125 times more toxic than glyphosate alone.[5]

Strong evidence indicates that surfactants or adjuvants disrupt cell membranes and initiate toxic changes to the mitochondria. Studies have shown that adjuvants have been found to exert their toxic effects through interfering with mitochondrial respiration.[3] One study of rat liver mitochondria found that Roundup suppressed mitochondrial Complexes II and III. Treatment of the mitochondria with the herbicide formulation resulted in uncoupling of oxidative phosphorylation, an effect not seen when the mitochondria were treated with glyphosate alone.[6]

Another study investigated the effects of Roundup or glyphosate alone on human buccal epithelial cells of the mouth in order to determine the effects of inhaling the herbicide. Roundup caused cellular membrane damage and mitochondrial dysfunction at levels greater than 40 mg/liter after 20 minutes. Glyphosate alone also was toxic to cellular membranes, but at double the concentration of Roundup used. Both Roundup and glyphosate caused DNA damage, even at lower doses, although Roundup was more toxic than glyphosate alone. Toxicity with Roundup was noted even after short exposure to concentrations 450 times more diluted than that sprayed on agricultural crops.[7]

Chronic Stress and the Mitochondria

Another modern-day cause of mitochondrial dysfunction is chronic stress. Although our ancient ancestors faced short-term stresses, such as an attack by a saber-tooth tiger, today we deal with chronic, ongoing stressors that take a toll on mitochondrial health.

Researchers have reported that chronic stress results in the production of too much nitric oxide, which could suppress mitochondrial respiratory chain function and trigger oxidative stress.[8] Chronic stress may also cause the mitochondria to produce an overwhelming amount of free radicals, which neurons aren't able to neutralize, causing mitochondrial dysfunction and neuronal cell death.[9]

Chronic stress can deplete the mitochondria's ability to produce energy. The brain is activated by stress, which can produce alterations in the brain's structure and function known as neuronal plasticity. The mitochondria must fuel these changes by producing additional energy. When the mitochondria are working the way they are supposed to, they are able to produce the energy demanded by stress-caused neuronal plasticity, protecting against the development of depression. However, when mitochondrial function is weakened, the brain's energy stores that are used up during stress are not replenished. This compromises neuronal plasticity and may increase the likelihood of developing depression.[10]

Fructose and Mitochondria

In the US, high-fructose corn syrup was introduced into the food supply in the 1970s. One of the mechanisms by which high-fructose corn syrup may induce type 2 diabetes and obesity is through its ability to cause mitochondrial dysfunction. Rats that were exposed to a high-fructose diet during gestation and lactation had impaired brain mitochondrial function in their old age and decreased mitochondrial phosphorylation efficiency.[11]

Fructose metabolism produces intermediary metabolites that overwhelm mitochondrial capacity in the liver, which can result in the development of hepatic insulin resistance. Additionally, fructose triggers formation of excessive reactive oxygen species, which can overwhelm the mitochondria.[12]

Some Medications Pose Another Threat

Many medications can cause mitochondrial dysfunction, which has emerged as the mechanism behind many side effects and toxicities of drugs. Some medications can directly affect electron transport chain complexes or damage electron transport chain components. Plus, medications can suppress enzymes necessary for mitochondrial function. In addition, some medications can

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trigger free radical production, depleting levels of antioxidants such as glutathione. Furthermore, pharmaceuticals can interfere with the absorption of nutrients that the mitochondrial electron transport chain complexes need for proper function.[13]

Many medications for angina, arrhythmia, depression, anxiety, high cholesterol (including statins), cancer, dementia, diabetes, HIV/AIDs, epilepsy, and Parkinson's can cause mitochondrial dysfunction. The antibiotics tetracycline and antimycin A, some barbiturates and anxiety medications, and anesthetics such as bupivacaine, lidocaine, and propofol are all toxic to the mitochondria. Even something as commonplace as aspirin and acetaminophen (Tylenol) can impair mitochondrial functioning.[13]

Epigenetic Involvement

The mitochondrial damage induced by the factors mentioned above can be transferred to children and grandchildren through epigenetics, heritable changes in gene expression that are not caused by changes in the DNA sequence.[14,15] The epigenetic modification of mitochondrial DNA may be responsible for the pathogenesis of many diseases.[16]

The Consequences of Mitochondrial Dysfunction

Mitochondrial dysfunction plays a role in the majority of today's most burdensome diseases – including aging itself.

Aging and the Mitochondria

The mitochondria contain members of gene family referred to as sirtuins, which are involved in longevity. Sirtuins are the conductors of the anti-aging orchestra. These genes control genetic, biochemical, and cellular pathways involved in aging.[17,18] Amplifying the expression of these genes is thought to increase longevity.[19,20]

The mitochondria contain three of the seven mammalian sirtuins, including SIRT3 and SIRT4.[21] Mitochondrial sirtuins may enhance longevity through mimicking caloric restriction, which protects against age-related disease and dysfunction, including cancer initiation.[22–26]

Beyond the sirtuins, an abundance of scientific evidence shows a strong connection between aging and mitochondrial dysfunction.[27–30] This evidence suggests that as mitochondria are exposed to a cumulative amount of reactive oxygen species and mitochondrial DNA damage, the burden becomes too much to bear, ultimately resulting in decreased lifespan.[26] With age, mitochondrial oxidative phosphorylation becomes less efficient.[31]

Cancer

Cancer is one of many diseases associated with mitochondrial dysfunction. The risk of developing cancer rises after age 50, which lends support to a potential link between mitochondrial processes involved in longevity and cancer development.[26,32,33] Furthermore, mitochondrial dysfunction in cancer cells is frequently noted in studies and coincides with abnormal cellular metabolism.[34,35] Researchers have found strong support for the likelihood that mitochondrial dysfunction plays an important role in cell transformation and carcinogenesis.[26]

Autistic Spectrum Disorders (ASD)

Mitochondrial dysfunction is well known to occur in autistic spectrum disorder.[36] The origin of this mitochondrial damage could be partially genetic. However, mitochondrial mutations are found in only 23% of ASD children diagnosed with mitochondrial dysfunction. Therefore, environmental causes such as exposure to heavy metals, exhaust fumes, polychlorinated biphenyls, or pesticides may be more important than genetic factors.[37] The oxidative stress caused by exposure to these toxins may serve as the link between mitochondria dysregulation and ASD.

Endogenous insults such as elevated pro-inflammatory cytokines resulting from an activated immune system could also damage the mitochondria in ASD patients.[38–40]

Other evidence of the presence of mitochondrial dysfunction in ASD patients is the fact that genes involved in the electron transport chain are downregulated (decreased Complex I, III, IV, and V). Genes involved in the citric acid cycle are also downregulated. Furthermore, mitochondrial DNA damage also has been noted in ASD patients.[41–43]

Mental Disorders

Mitochondrial dysfunction is an underappreciated component of various mental disorders. Bipolar patients experience reduced levels of Complex I of the electron transport chain.[44] Patients suffering from major depression also have abnormalities in Complex I.[45] Similarly, researchers have noted a significant decrease in Complex I activity in schizophrenia patients along with a drop in CoQ10 levels.[46] Mitochondrial abnormalities also have been noted in subjects with obsessive-compulsive disorder.[47]

Cardiovascular Concerns

Mitochondrial dysfunction is a key player in age-related damage to the heart. The heart has a high metabolic demand and contains a large number of mitochondria. Because ROS is produced in the mitochondria through oxidative phosphorylation, the heart is particularly vulnerable to oxidative damage.[31]

Other evidence for mitochondrial dysfunction's association with cardiovascular disease includes the existence of mitochondrial dysregulation and mtDNA mutations in atherosclerotic plaques.[48–51]

According to one group of researchers, "Development of novel therapeutic approaches for mitochondrial rejuvenation and attenuation of mitochondrial oxidative stress holds promise for reducing cardiovascular mortality in an aging population."[31]

Mitochondrial dysfunction has been associated with the metabolic syndrome (a cluster of risk factors for cardiovascular disease) providing another reason why mitochondrial abnormalities may damage the heart.[52–56]

Type 2 Diabetes

Diabetes is marked by mitochondrial dysfunction and high oxidative stress levels.[57] Persistently high blood sugar levels harm both mitochondria and mitochondrial DNA.[58] Diabetic patients often experience downregulation of Complex I and/or IV and type 2 diabetes occurs side by side with some diseases related directly to mitochondrial dysfunction such as the genetic diseases Fanconi anemia and Werner syndrome.[59–65]

Neurodegenerative Diseases

Studies strongly suggest that mitochondria abnormalities may be linked to the development of several neurodegenerative diseases such as Parkinson's disease, Alzheimer's, Friedreich's ataxia, multiple sclerosis, amyotrophic lateral sclerosis, and Huntington's disease.[8] Rat models of Parkinson's disease indicate that reactive oxygen species interfere with mitochondrial processes.[65] Researchers have found that mitochondrial abnormalities caused by amyloid-beta occur early in Alzheimer's disease.[66–72]

Other Diseases Linked to Mitochondrial Dysfunction

In terms of diseases related to mitochondrial dysfunction, what we've discussed in this article so far is just the tip of the iceberg. For example, mtDNA damage has been noted in osteoarthritis along with downregulated Complexes I, II, and III, and 17 upregulated and 9 downregulated genes.[73–75] Furthermore, in autoimmune diseases antimitochondrial autoantibodies (AMA) can damage the mitochondria.[78] Autoimmune diseases associated with mitochondrial dysfunction include vitiligo, systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, primary biliary cirrhosis, and psoriasis.[76]

Additionally, researchers have attributed the damage done by obstructive sleep apnea (OSA) to mitochondrial dysfunction. In OSA patients there is a decrease in mtDNA copy number, which is linked to oxidative stress and inflammation.[77]

Other diseases related to mitochondrial dysfunction include cataracts, fibromyalgia, and non-alcoholic fatty liver disease.[76]

The Hormonal Link

When supporting optimal hormonal health amongst patients, it is essential to consider the mitochondrial health and function of the target endocrine tissues being treated. Fueling the target mitochondrial cells can dramatically augment therapeutic outcomes. This is because there is an intricate interplay between hormones and mitochondria.[77–85] Hormones originate in the mitochondria where cholesterol is converted to pregnenolone, the precursor to all steroid hormones.[78,79] The mitochondrial electron transport chain also plays a role in producing testosterone in the Leydig cells.[80]

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Furthermore, receptors for estrogens, androgens, and thyroid hormones are located in the mitochondria.[81,82] Estrogens and androgens also are able to shield the mitochondria from damage and estrogen is involved in many aspects of mitochondrial function and biogenesis, including oxidative phosphorylation.[83–86]

Diagnosing Mitochondrial Dysfunction

Along with clinical observations, an organic acid test is often used to diagnose mitochondrial dysfunction. Organic acids are produced as a result of the breakdown of proteins, carbohydrates, and fats. These acids serve as intermediates in the citric acid (Krebs) cycle.

The presence or elevation of specific organic acids can serve as a marker for mitochondrial abnormalities or indicate exposure to toxins that may harm the mitochondria. For example, 4-hydroxybenzoic acid and 4-hydroxyhippuric acid are metabolites of parabens, toxic compounds found in lotions, cosmetics, other toiletries, and even food.[87,88] Parabens may impair oxidative phosphorylation, resulting in mitochondrial dysfunction.[89] An organic acid test can determine if 4-hydroxybenzoic acid and 4-hydroxyhippuric acid are elevated.

Another example is the organic acid adipic acid (adipate). If the value is elevated it can indicate functional deficiency of carnitine. A deficiency of carnitine can stop long chain fatty acids from entering the mitochondria. This results in insufficient fatty acid oxidation. Organic acid tests also can measure a marker of CoQ10 production.

When interpreting organic acid test results, it is important to be familiar with all the nuances, because some foods and drugs as well as fasting can affect the results.[90]

Functional micronutrient testing also is important, because the pathways critical for ATP production need to be fueled by key nutrients. A deficiency in these nutrients can compromise mitochondrial health.

Clinical Considerations in Treating Mitochondrial Dysfunction

Because mitochondrial dysfunction has emerged as a key player in a host of different diseases, it makes sense to include a mitochondrial support component in wellness regimens.

From a lifestyle perspective, a ketogenic diet may enhance mitochondrial health in children with autistic spectrum disorder and epilepsy. A ketogenic diet is a high-fat diet with enough protein for growth but not enough carbohydrates for metabolic needs. This type of diet causes the body to use fat as its main source of fuel. A ketogenic diet has been shown to improve various aspects of mitochondrial function during in vitro, in vivo, and human studies.[91–95] However, one problem with the ketogenic diet is that it is low in vegetables. The antioxidants in vegetables protect against excess reactive oxygen species generated by mitochondrial dysfunction, hence demanding consideration of supplemental antioxidant protection when consuming a ketogenic diet.

Research indicates moderate exercise also is critical to mitochondrial health. For example, in one mouse model of non-alcoholic steatohepatitis, mitochondrial abnormalities in the liver disappeared after the animals underwent endurance exercise.[96]

Fueling the Mitochondria

A number of the components required for oxidative phosphorylation need to be frequently replaced. This can be accomplished with supplementation of key nutrients such as L-carnitine, alpha-lipoic acid, coenzyme Q10, creatine monohydrate, and N-acetylcysteine (NAC), which have all been shown to be of benefit.[97]

Mitochondrial bioenergetic enzymes require alpha-lipoic acid, a critical cofactor. In rodent and cell culture studies, alpha-lipoic acid has been found to restore mitochondrial biogenesis, to reduce mitochondrial deformation and intracellular ROS production, and to increase intracellular ATP synthesis and mitochondrial DNA numbers.[98,99]

One randomized, double-blind clinical trial that used a combination of creatine monohydrate, coenzyme Q10, and alpha-lipoic acid lowered markers of oxidative stress in people with mitochondrial cytopathies while creatine monohydrate used alone in patients with mitochondrial encephalomyopathies enhanced aerobic oxidative function of the mitochondria.[100,101]

L-carnitine also is important to mitochondrial health because it helps transfer long-chain fatty acids from the cytoplasm of the cell to the mitochondria. During carnitine deficiency, there are less fatty acids available for energy production, resulting in symptoms such as myalgia and muscle weakness.[102] It's therefore not surprising that acetyl-L-carnitine (ALC), which is created from acetylation of carnitine in the mitochondria, is a powerful mitochondrial rejuvenator. When paired with alpha-lipoic acid in a nonalcoholic fatty liver mouse model, ALC enhanced the content and size of the mitochondria in the liver.[103] ALC supplementation also promoted the formation of new mitochondria in the livers of old rats, which helped reduce oxidative stress.[104]

Another component of a mitochondrial rejuvenation regimen is the glutathione precursor N-acetylcysteine, researched for its ability to enhance mitochondrial health. In one study of rats with spinal cord injuries, NAC improved mitochondrial bioenergetics and maintained mitochondrial glutathione levels near normal.[105]

Supplementing with citric acid cycle metabolites such as malate, succinate, and alpha-ketoglutarate can also be of benefit.[106]

Other Mitochondrial Rejuvenators

New studies are showing several other natural agents may have mitochondrial-restoring effects. Evidence is mounting that resveratrol can improve mitochondrial activity. In cells from patients with early onset Parkinson's disease, resveratrol enhanced mitochondrial oxidative

function, which researchers believe is due to a decrease of oxidative stress and increased mitochondrial biogenesis. Resveratrol increased Complex I and citrate synthase activities, basal oxygen consumption, and mitochondrial ATP production.[107]

In other studies, resveratrol prevented mitochondrial dysfunction in a rat model of diabetic cardiomyopathy and increased cell survival after traumatic brain injury, in part by protecting the mitochondria.[108,109]

Surprisingly, glucosamine also emerged as a possible mitochondrial protector when a study published in 2014 showed that glucosamine extends the lifespan of both the nematode *Caenorhabditis elegans* and aging mice in part by enhancing mitochondrial biogenesis.[110]

Other nutrients shown to enhance mitochondrial function include quercetin, green tea, and omega-3 fatty acids.[111–114]

Conclusion

In treating any health condition and improving overall foundational well-being, we can't forget to look at the proverbial "Energizer bunny" batteries of the trillions of cells that comprise the human frame. Mitochondrial dysfunction is the driving force behind the development or symptom severity in many diseases. Given the widespread involvement the mitochondria have in disease, incorporating nutrients that fuel mitochondrial pathways into any wellness-oriented supplement regimen is key to restoring whole body health. Due to the role hormones play in mitochondrial health – and vice versa – nourishing the mitochondria during hormone replacement therapy also is advised. Bottom line: unfueled cells are destined to underperform.

Notes

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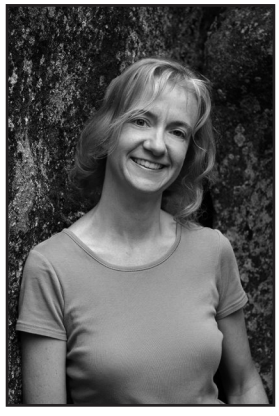
Dr. Chris D. Meletis is an educator, international author, and lecturer. His personal mission is "Changing America's Health One Person at a Time." He believes that when people become educated about their bodies, that is the moment when true change and wellness begins. Dr. Meletis served as dean of naturopathic medicine and chief medical officer for 7 years at National College of Natural Medicine (NCNM) and was awarded the 2003 Physician of the Year award by the American Association of Naturopathic Physicians. www.DrMeletis.com.



Kimberly Wilkes is a freelance writer specializing in health, science, nutrition, and complementary medicine. She has written more than 300 articles covering a variety of topics from the dangers of homocysteine to sugar's damaging effects on the heart. She is the editor of *Complementary Prescriptions Journal* and enjoys scouring the medical literature to find the latest health-related science.