The Complex Interplay between Mitochondria and Oxidative Stress

DEBBY HAMILTON, M.D., MPH
Objectives

1. Understand mitochondrial function and how the formation of reactive oxygen species is a normal part of the process but damaging in excess
2. Learn about the unique vulnerability of mitochondria to oxidative stress
3. Review environmental factors that contribute to mitochondrial dysfunction and oxidative stress
4. Discuss diseases associated with mitochondrial dysfunction and oxidative stress
5. Discuss nutritional support for mitochondrial function and oxidative stress
WHY?
Mitochondrial Disease versus Mitochondrial Dysfunction

- **Mitochondrial Disease:**
  - Genetic disorder of mitochondria: Can be acquired or spontaneous mutation

- **Mitochondrial dysfunction**
  - Increase in oxidative stress from environmental stressors causing mitochondrial

- Treatment is **supportive** and the **same** for both disease and dysfunction
Mitochondrial Disease

- If 3 or more organ system involved consider mitochondrial disease
  - Seizures, stroke, severe developmental delay, dysautonomia, hypotonia, dysmotility (gastrointestinal diseases), cardiomyopathy, renal tubular acidosis, fatigue, failure to thrive, hearing loss, hypoglycemia, inability to walk, dementia

- Syndromes: examples: Leigh Disease, MELAS (mitochondrial encephalomyopathy lactic acidosis and stroke like episodes), complex 1 deficiency, Leukodystrophy, cytochrome oxidase deficiency
Mitochondrial Dysfunction symptoms

- Intellectual Disability/Development Delay/ASD
- Seizure Disorders
- GI
- Autonomic Dysfunction (e.g., CVS)
- Muscle Myopathy
- Pain
- Fatigue
Energy Crisis!
Mitochondria: Fast Facts

- Mitochondria make 90% of cell’s ATP
- Every cell has hundreds of mitochondria
- Mitochondria has its own DNA called mtDNA that code for 37 genes
- mtDNA code for RNA and polypeptides essential for the electron transport chain and formation of ATP
- mtDNA: 10 times more susceptible to mutation and damage from oxidative stress than nuclear DNA
Mitochondrial Function

1. ATP production—produce energy for the cell
2. Initiating and performing apoptosis and cell death
3. Calcium homeostasis
4. Iron homeostasis
Breakdown of food into components for the Krebs or TCA cycle
Note: Compounds Reported in the ION™ Profile are Printed in Colors.
Vitamin & mineral requirements for enzyme cofactors are shown in light blue boxes.
Elevations of metabolites before these steps indicate functional deficiency of the nutrients.
Amino acids are shown in white oval boxes.
Proteins in the electron transport chain: Process of oxidative phosphorylation

- Complex I: NADH (niacinamide or NADH)
- Complex II: FADH2 (Riboflavin or B2)
  - Electrons passed from above to CoQ10
- Complex III: Cytochrome C
  - CoQ10 give electrons to cytochrome C
- Complex IV:
  - Adds electrons to oxygen to create H2O
- Complex V: ATP synthase
  - Formation of ATP from ADP
Proteins in the electron transport chain

Electron Transport Chain

Intermembrane space

Mitochondrial matrix

Inner mitochondrial membrane

NADH → FADH₂ → Q → FAD → Cyt c → H₂O

NAD⁺ + H⁺ → 2H⁺ + 1/2O₂

Researched Nutritionals®
Mitochondria naturally produce free radicals:
- Superoxide
- Hydrogen peroxide
- Hydroxyl radicals
Oxygen and other Reactive Oxygen Species

- $\text{O}_2$: Oxygen
- $2\text{O}_2^- \xrightarrow{e^-} 2\text{O}_2^-$: Superoxide anion
- $2\text{O}_2^- \xrightarrow{2e^- + 2\text{H}^+} 2\text{H}_2\text{O}_2$: Hydrogen peroxide
- $\text{H}_2\text{O}_2 \xrightarrow{e^- + \text{H}^+} 2\cdot\text{OH}$: Hydroxyl radical

- $\cdot\text{O} = \cdot\text{H}$: Hydroxyl radical
Oxidative Stress

Definition

Imbalance between the production of free radicals and the ability of the body to counteract or detoxify their harmful effects through neutralization by antioxidants.
Oxidative Stress

Free radical chain reaction is much like this.
Oxidative Stress

Free radical chain reaction is much like this.
Oxidative Stress Damage to Mitochondria

- Mitochondrial DNA (mtDNA)
- Mitochondrial lipids
  - Cardiolipin: releases cytochrome C into cytosol, starts apoptosis
- Mitochondrial protein alteration
  - Aconitase:
    - key role in Krebs cycle transfer citrate to isocitrate
    - Inactivation of Fe-S releases Fe and H2O2 leading to formation of hydroxyl radical
  - Uncoupling protein 2

Cycle of mitochondria and oxidative stress

- Oxidative stress causes damage to mtDNA
- Damaged mtDNA leads to decrease in coding for proteins needed for electron transport chain
- Decreased function of electron transport chain leads to decreased energy and increased free radicals (oxidative stress)
- Increased oxidative stress causes damage to the cell membrane
- Damage to the cell membrane leads to release of cytochrome C leading to apoptosis or cell death
- Cell death leads to more oxidative stress

.........And the cycle continues
Causes of Damage to Mitochondria

- **Mitochondrial Dysfunction**
  - Medicines
  - Poor Nutrition
  - Stress
  - Pesticides (Glyphosate)
  - Heavy Metals
  - Environmental toxins

- **Oxidative Stress**
  - Medicines
  - Poor Nutrition
  - Stress
  - Pesticides (Glyphosate)
  - Heavy Metals
  - Environmental Toxins
### Medications That Cause Mitochondrial Dysfunction

Mitochondrial dysfunction is to blame for many toxicities caused by drugs and may explain the side effects of many medications. Even so, the Food and Drug Administration doesn’t require mitochondrial toxicity testing for new drug approval.

Drugs can damage mitochondria in two ways: directly or indirectly. Medications can directly inhibit mtDNA transcription of electron transport chain complexes. Through other mechanisms, medications damage electron transport chain components, as well as block enzymes required for mitochondrial function.54

Indirect mitochondrial damage caused by medications occurs through the production of free radicals, causing a decrease in endogenous antioxidants such as glutathione. Medications may also deplete levels of nutrients needed for creating or proper functioning of mitochondrial enzymes or electron transport chain complexes.54

### Medications Documented to Cause Mitochondrial Damage54

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism medications</td>
<td>Disulfiram (Antabuse)</td>
</tr>
<tr>
<td>Analgesic (for pain) and anti-inflammatory</td>
<td>Aspirin, acetaminophen (Tylenol®), diclofenac (Voltaren®, Voltarol®, Diclofen®, Diclofen®, Difen, and Cataflam®), fenoprofen (Nalfon®), indomethacin (Indocin®, Indocid®, Indocron E-R® Indocin-SR®), Naproxen (Aleve®, Naprosyn®)</td>
</tr>
<tr>
<td>Anesthetics</td>
<td>Bupivacaine, lidocaine, propofol</td>
</tr>
<tr>
<td>Angina medications</td>
<td>Perhexiline, amiodarone (Cordarone®), Diethylaminoethoxyhexesterol (DEAHE)</td>
</tr>
<tr>
<td>Antiarrhythmic (regulates heartbeat)</td>
<td>Amiodarone (Cordarone®)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Tetracycline, antimycin A</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline (Lentizol), amoxapine (Asendis), citalopram (Cipramil), fluoxetine (Prozac, Symbyax, Sarafem, Fontex, Foretin, Ladoxe, Fluclot, Prodep, Fludac, Osetin, Seronil, Lovan)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Chlorpromazine, fluphenazine, haloperidol, risperidone,quetiapine, clozapine, olanzapine</td>
</tr>
<tr>
<td>Anxiety medications</td>
<td>Alprazolam (Xanax®), diazepam (valium, diastat)</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Amobarbital (Amytal®), aprobarbital, butabarbital, butalbital (Fiorinal®), hexobarbital (Sombulex®), methylphenobarbital (Mebaral®), pentobarbital (Nembutal®), phenobarbital</td>
</tr>
<tr>
<td>(Luminal®, primidone, propofol, secobarbital (Secoda®), Talbutal®, thiobarbital)</td>
<td>Mitomycin C, proflomycin, adriamyacin (also called doxorubicin and hydroxydaunorubicin and included in the following chemotherapeutic regimens – ABVD, CHOP, and FAC)</td>
</tr>
<tr>
<td>Cholesterol medications</td>
<td>Statins –atorvastatin (Lipitor®), Torvast®, fluvasatin (Lescol®), lovastatin (Mevacor®), Altocor®, pitavastatin (Livalo®), Pitav®, pravastatin (Pravachol®), Selctine® Brand, Lipostat®, rosuvastatin (Crestor®), simvastatin (Zocor®), Lipex® bile acids – cholestyramine (Questran®), clofibrate (Atromid-S®), ciprofibrate (Modalan®), colestipol (Colestid®), colesalva (Welcho®)</td>
</tr>
<tr>
<td>Cancer (chemotherapy) medications</td>
<td>Mitomycin C, proflomycin, adriamyacin (also included doxorubicin and hydroxydaunorubicin and included in the following chemotherapeutic regimens – ABVD, CHOP, and FAC)</td>
</tr>
<tr>
<td>Dementia</td>
<td>Tacrine (Cognex®), Reminyl®</td>
</tr>
<tr>
<td>Diabetes medications</td>
<td>Metformin (Fortamet®, Glucophage®, Glucophage XR, Riomet), troglitazone, rosiglitazone, buformin</td>
</tr>
<tr>
<td>HIV/AIDS medications</td>
<td>Atripla®, Combid® , Emtriva®, Epivir® (abacavir sulfate), Epzicom®, Hivid® (ddI, zalcitabine), Retrovir® (AZT, ZDV, zidovudine), Trizivir®, Truvada®, Vides® (ddI, didanosine), Vides® FC, Viracid®, Zerit® (ddI, stavudine), Ziaqor®, Racic®</td>
</tr>
<tr>
<td>Epilepsy/Seizure medications</td>
<td>Valproic acid (Depacon®, Depakene®, Depakene syrup, Depakote®, depakote ER, depakote sprinkle, divalproex sodium)</td>
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<tr>
<td>Mood stabilizers</td>
<td>Lithium</td>
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<tr>
<td>Parkinson’s disease medications</td>
<td>Tolcapone (Tasmar®), Entacapone (COMTAn®, also in the combination drug Stalevo®)</td>
</tr>
</tbody>
</table>
In conclusion, a fructose-rich diet leads to mitochondrial and mtDNA damage, which consequently may have a role in liver dysfunction and metabolic diseases.

Fructose-Rich Diet Affects Mitochondrial DNA Damage and Repair in Rats.

Cioffi MW. Et al.. Nutrients. 2017 March.
Diagnosis

- Quantitative urine organic acids
- Blood Lactate and pyruvate
- Plasma Acyl-carnitine profile
- CoQ10 levels
- Liver enzymes and ammonia
- Quantitative amino acids
- Creatinine kinase

- Mitochondrial Disease: additional testing
  - muscle biopsy, genetic profiles, echocardiogram, analysis of cerebral spinal fluid
Neurodegenerative diseases: Progressive Diseases with mitochondrial damage and oxidative stress

- 5 million Americans suffer from Alzheimer's disease
- 1 million from Parkinson's
- 400,000 from multiple sclerosis (MS)
- 30,000 from amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease)
- 30,000 from Huntington's

If left unchecked 30 years from now, more than 12 million Americans will suffer from neurodegenerative diseases.

http://neurodiscovery.harvard.edu/challenge
Abstract: Neurodegenerative diseases are incurable and devastating neurological disorders characterized by the progressive loss of the structure and function of neurons in the central nervous system or peripheral nervous system. Mitochondria, organelles found in most eukaryotic cells, are essential for neuronal survival and are involved in a number of neuronal functions. Mitochondrial dysfunction has long been demonstrated as a common prominent early pathological feature of a variety of common neurodegenerative diseases, including Alzheimer’s disease (AD), Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington’s disease (HD). Mitochondria are highly dynamic organelles that undergo continuous fusion, fission, and transport, the processes of which not only control mitochondrial morphology and number but also regulate mitochondrial function and location. The importance of mitochondrial dynamics in the pathogenesis of neurodegenerative diseases has been increasingly unraveled after the identification of several key fusion and fission regulators such as Drp1, OPA1, and mitofusins. In this review, after a brief discussion of molecular mechanisms regulating mitochondrial fusion, fission, distribution, and trafficking, as well as the important role of mitochondrial dynamics for neuronal function, we review previous and the most recent studies about mitochondrial dynamic abnormalities observed in various major neurodegenerative diseases and discuss the possibility of targeting mitochondrial dynamics as a likely novel therapeutic strategy for neurodegenerative diseases.
Children with autism were more likely to have mitochondrial dysfunction, mtDNA over replication, and mtDNA deletions than typically developing children.

Giolivi C. et al. Mitochondrial dysfunction in autism
JAMA. 2010 December 1; 304(21): 2389–2396.
Down's syndrome (DS), which is characterized by premature aging, that there is enhanced oxidative stress resulting from the aberrant expression of CuZn superoxide dismutase (CuZn SOD).

Down's syndrome: increased aging associated with repaired anti-oxidant defense in the mitochondria

Defective repair of oxidative damage in mitochondrial DNA in Down's syndrome. Druzhyna N. Et al. Mutation Research
Mitochondrial dysfunction in FMS/FMD

Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: implications in the pathogenesis of the disease

Mario D. Cordero1,2, Manuel De Miguel1, Ana M. Moreno Ferrándiz2, Inda V. Carranza López2, Juan García Maraver1, David Cotoán1,2, Laura Sánchez Barreda, Pablo Porras1, Francisco Campa1, Pedro Buil1,2, Pilar Noval1,2 and José A. Sánchez Arce1,2

Abstract

Introduction: Fibromyalgia is a chronic pain syndrome with an unknown etiology. Recent studies have shown some evidence demonstrating that oxidative stress may have a role in the pathophysiology of Fibromyalgia. However, it is still not clear whether oxidative stress is the cause or the effect of the abnormalities documented in Fibromyalgia. Furthermore, the role of mitochondria in the redox imbalance reported in Fibromyalgia is also controversial. We undertook this study to investigate the role of mitochondrial dysfunction, oxidative stress, and mitophagy in Fibromyalgia.

Methods: We studied 20 patients (12 male, 8 female) and 10 healthy controls. We evaluated mitochondrial dysfunction in Fibromyalgia patients measuring coenzyme Q10 levels - mitochondrial membrane potential with flow cytometry superoxide production with MitoSOX® and lipid peroxidation by malondialdehyde (MDA) levels. Mitophagy activation was evaluated by electron microscopy examination of blood mononuclear cells. Mitophagy was measured by electron microscopy examination of blood mononuclear cells.

Results: We found reduced levels of coenzyme Q10, mitochondrial membrane potential, increased levels of mitochondrial superoxide in blood mononuclear cells, and increased levels of lipid peroxidation in both blood mononuclear cells and plasma from fibromyalgia patients. Mitochondrial dysfunction was also associated with increased expression of autophagic genes and the elimination of dysfunctional mitochondria with mitophagy.

RESULTS: We found reduced levels of coenzyme Q10, decreased mitochondrial membrane potential, increased levels of mitochondrial superoxide in blood mononuclear cells, and increased levels of lipid peroxidation in both blood mononuclear cells and plasma from fibromyalgia patients. Mitochondrial dysfunction was also associated with increased expression of autophagic genes and the elimination of dysfunctional mitochondria with mitophagy.
Evidence has been gathered to suggest that an elevation of oxidative stress and associated oxidative damages gradually occur in the mitochondria of tissue cells during aging.

Mitochondria and ageing: role in heart, skeletal muscle and adipose tissue

Ageing

- reduced protein expression
- reduced enzyme activity
- reduced DNA content
- reduced turnover
- reduced biogenesis
- morphological changes
- reduced calcium release units
- DNA damage/mutations
- impaired dynamics

Progression of Sarcopenia

+ sedentary lifestyle

- increased cytochrome oxidase activity
- increased antioxidant defense
- enhanced function
- increased biogenesis
- preserved calcium release units
- less DNA damage
- improved dynamics

Attenuation of Sarcopenia

+ training
Support for mitochondrial dysfunction and oxidative stress

- Repair and support mitochondria
  - Membrane repair
  - Support nutrients in ATP production from breakdown of macronutrients to Krebs cycle to oxidative phosphorylation

- Decrease oxidative stress

- Increase anti-oxidants to counteract oxidative stress
Support for mitochondrial dysfunction and oxidative stress

- Repair mitochondrial membrane
  - Phospholipids
Support for mitochondrial dysfunction and oxidative stress

- Repair mitochondrial membrane
  - Phospholipids
- Support mitochondrial function
  - CoQ10/Ubiquinol
  - Carnitine
  - NADH
  - Alpha-lipoic acid
  - B vitamins
  - Vitamin E
Phospholipid delivery system for mitochondrial membrane repair plus optimization of Krebs Energy Cycle

Top mitochondrial nutrients:
- Unique Phospholipid Matrix: repair mitochondrial membrane
- Stabilized NADH
- CoQ10
- Carnitine
- Vitamin E
- Alpha-ketoglutaric acid
ATP Fuel®
Clinical Research Highlights

- 58 patient (Lyme, CFS, Fibromyalgia) study
- 31% fatigue reduction
- 30% cognitive function improvement

Published in peer reviewed journals
- *International Journal of Clinical Medicine*
- *Functional Foods in Health & Disease*
Support for mitochondrial dysfunction and oxidative stress

- Repair mitochondrial membrane
  - Phospholipids
- Support mitochondrial function
  - CoQ10/Ubiquinol, Carnitine, NADH, B vitamins, Alpha-Lipoic Acid, Vitamin E
- Anti-oxidants to combat oxidative stress
  - Molecular Hydrogen (H₂: Hydrogen gas)
  - Vitamin E: mixed tocopherols and tocotrienols
  - Curcumin
  - Tea: EGCG
  - Resveratrol
  - Glutathione
  - N-acetyl-cysteine
Hydroxyl Radical

- The most dangerous free radical in the body
- It will attack most cellular components
  - reacts with nucleic acids, lipids and proteins
  - There is no known Hydroxyl Radical detoxification system in the body
  - scavenging Hydroxyl Radical is a critical antioxidant process

Oxygen and other Reactive Oxygen Species

- Oxygen: $\ce{O2}$
- Superoxide anion: $\ce{O2^-}$
- Peroxide: $\ce{O2^{2-}}$
- Hydroxyl radical: $\ce{•OH}$

Chemical reactions:

\[ \ce{O2 + e^-} \rightarrow \ce{2O2^-} \quad \text{Superoxide anion} \]
\[ \ce{2O2^- + 2e^- + 2H^+} \rightarrow \ce{2H2O2} \quad \text{Hydrogen peroxide} \]
\[ \ce{H2O2 + e^- + H^+} \rightarrow \ce{2•OH} \quad \text{Hydroxyl radical} \]
Molecular Hydrogen
Hydrogen Gas (H₂)

- Hydrogen gas is very stable molecule
- Neutralizes harmful free radicals, including the hydroxyl radical
  - Hydrogen electron donation turns hydroxyl into water
- Diffuses across membranes, including mitochondria, due to its small size
  - Most antioxidant supplements are limited in their cellular distributions and are poorly taken up by organelles like mitochondria
  - Hydrogen has the ability to effectively penetrate biomembranes and infiltrate into organelles, such as mitochondria and the nucleus
  - In contrast to many antioxidants, H₂ also has the advantage of being able to penetrate the blood-brain barrier

2 Molecular hydrogen as a preventive and therapeutic medical gas: initiation, development and potential of hydrogen medicine, Ohta S., Pharmacology & Therapeutics, Volume 144, Issue 1, October 2014, Pages 1–11
3 Clinical Effects of Hydrogen Administration: From Animal and Human Diseases to Exercise Medicine, Nicolson G. et al., International Journal of Clinical Medicine, 2016, 7, 32-76

Researched Nutritionals®
Molecular Hydrogen: H₂

Summary

1.) Anti-oxidant for dangerous hydroxyl radical without destroying free radicals needed for metabolism

2.) Activates Nrf2 anti-oxidant cascade including glutathione peroxidase, catalase, and superoxide dismutase (SOD)

3.) Decreases pro-inflammatory cytokines through cell signaling

4.) Promotes mitochondrial ATP energy function

1Molecular hydrogen as a preventive and therapeutic medical gas: initiation, development and potential of hydrogen medicine, Ohta S., Pharmacology & Therapeutics, Volume 144, Issue 1, October 2014, Pages 1-11

2Clinical Effects of Hydrogen Administration: From Animal and Human Diseases to Exercise Medicine, Nicolson G. et al., International Journal of Clinical Medicine, 2016, 7, 32-76

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Dr. Debby Hamilton, MD, MPH
Researched Nutritionals®

Email: dh.hamilton@ResearchedNutritionals.com

Web: www.researchednutritionals.com
Appendix

- Suggested Protocols
- CoQ10
- Carnitine
- References
Suggested Protocols: First Line therapy

1: **First line energy- mitochondrial support:**
ATP Fuel™

**First line support for adrenal weakness:**
Energy Multi-Plex™:

* Begin together for more severe fatigue support*
Suggested Protocols: Second Additions

2: For extra CoQ10 support:

Add CoQ10 Power™ or Ubiquinol Super 200™

and/or

For extra carnitine support and cardiovascular health and exercise use:

Add RiboseCardio™
Energy-Mitochondrial Nutritional Support

ATP Fuel™: *First line energy-mitochondrial support*

NT factor lipids and stabilized NADH with additional mitochondrial support from targeted vitamins, minerals, amino acids, and metabolic co-factors (CoQ10, carnitine)

*Use:* 5 capsules 2 times a day before meals for 2 months to optimally repair cell membranes and then 5 capsules daily

Energy Multi-Plex™: *First line support for adrenal weakness*

support for adrenals from targeted vitamins, minerals, herbs, amino acids, and metabolic co-factors (CoQ10, Carnitine)

*Use:* 3 capsules daily
Energy-Mitochondrial Nutritional Support

CoQ10 Power™ or Ubiquinol Super 200™: targeted high dose CoQ10 supplement

Use: 1 to 2 capsules daily (up to 3 for CoQ10 Power™) with meals

RiboseCardio™: for cardiovascular health and exercise support with ribose sugar and high dose carnitine

Use: 1 scoop 2 times a day (up to 4 scoops daily) before 3 pm
Support for mitochondrial dysfunction, oxidative stress and Inflammation

- ATP Fuel®
- CytoQuel®
- H2Absorb™

- Additional support:
  - CoQ10 Power™
  - Ribose Cardio™
  - C-RLA™: Liposomal vitamin C and R-lipoic acid
  - Tri-Fortify™ Liposomal glutathione
CytoQuel®
healthy cytokine support

- **Black Tea Extract**
  - Much stronger antioxidant than green tea
  - Highest EGCG Content - 50%

- **CurcuWin®**
  - 46X absorption of standard curcumin*
  - 35X absorption of BCM-95®*
  - 6X absorption of Meriva®*

- **Delta Gold® Tocotrienols**
  - Pure delta & gamma
  - No tocopherols = better absorption

- **N-Acetyl-cysteine (NAC)**

- **Resveratrol (Natural Trans-Resveratrol)**

CytoQuel®
healthy cytokine support

- **Suggested Use**
  - Take one capsule per day with a meal for the first week, and three capsules per day with a meal in week two and beyond, or use as directed by your healthcare professional.
  - They may be taken at the same meal or spread amongst your meals.
  - For best results take away from Vitamin E (tocopherol).
  - Herx response suggested use: 2 bid
**Suggested Use**

- As a dietary supplement, place one tablet in a bottle of non-carbonated water and replace cap immediately. Wait until tablet has dissolved in water before consuming. We recommend an 8 ounce (240 ml) bottle so one may consume the water with fewer opening/closings of the bottle, delivering the maximum amount of hydrogen gas to the body.

- For best results, be sure the bottle is completely full of water (with little or no air space at the top). Follow this procedure twice daily or as recommended by your healthcare professional.

- Product may be taken with or without food.
CoQ10

**Functions:**
- Needed in the mitochondria to make ATP as part of the electron transport chain
- Fat-soluble anti-oxidant which inhibits lipid peroxidation to protect membrane proteins and DNA
- Regenerates active forms of Vitamin E and Vitamin C

**Location:** highest in the heart, brain, kidneys, liver (high energy needs)
- Natural compound made in the body so high safety profile

**Testing for CoQ10:** Blood CoQ10 level best with genetic deficiency although low range of normal levels may need CoQ10. Urine organic acid test (OAT) test for Krebs Cycle metabolites: markers for decreased CoQ10
Decreased Levels may be of CoQ10 may be associated with

- Poor diet
- Aging
- Increased metabolic and energy needs
  - example: heart disease and vascular disease because the heart has high energy needs
- Increased oxidative stress
- Medicines that decrease CoQ10 such as lipid lowering statins, anesthetics, chemotherapy
- Hypotonia (low muscle tone)
- Mitochondrial dysfunction
- Male infertility
Products containing CoQ10

- ATP Fuel®
- Energy Multi-Plex™
- CoQ10 Power™
- Ubiquinol Super 200™
- Physician’s Daily™
Carnitine

**Functions:** Transports long-chain fatty acids into the mitochondria to aid in the cellular energy production of ATP. Transports toxic compounds out of the mitochondria to prevent their accumulation. Highest concentration in cardiac and skeletal muscle.

**Forms:** L-Carnitine, Acetyl L-Carnitine, and propionyl L-Carnitine (this form not often in supplements). Amino acid made in the body so high safety profile.

**Side Effects:** high doses may have digestive side effects such as diarrhea with > 3gms/day seen more with the L-Carnitine form as opposed to the Acetyl L-Carnitine form. High doses can get a fishy odor. Energy supplement so use in the morning/mid-day.

**Testing:** Acylcarnitine profile in blood (total carnitine, free carnitine, acylcarnitine) best for detecting carnitine genetic defects. Urine organic acid tests (OAT) for fatty acid metabolites: markers for decreased carnitine levels.

Researched Nutritionals®
Decreased levels of Carnitine may be associated with:

- Aging
- Mitochondrial dysfunction
- Hypotonia (low muscle tone)
- Cognitive impairment
- Medications that decrease carnitine: examples: anti-seizure medicines such as Depakote, Phenytoin, Carbamazepine; some chemotherapy medicines and HIV medicines
- Increased oxidative stress
- Increased energy needs
- Vegetarians/Vegans (carnitine is in animal products)
- Weak heart or skeletal muscle
- Male infertility
Products containing Carnitine:

- ATP Fuel®
- NT Factor® Energy
- Energy Multi-Plex™
- RibosCardio™
- CogniCare™
References for CoQ10


Researched Nutritionals®
References for Carnitine:


References for Carnitine:


References for Molecular Hydrogen

- Molecular hydrogen foundation: www.molecularhydrogenfoundation.com
Tocotrienols: Part of Vitamin E group of nutrients

- Rondanelli M. Et al. Focus on pivotal role of dietary intake (diet and supplements) and blood levels of tocopherols and tocotrienols in obtaining successful aging. In J Mol Sci. 2015;16, 23227-23249.

Research with combination of ingredients in CytoQuel®

- **Resveratrol, Curcumin, Vitamin E, Tea (EGCG), and N-Acetyl-Cysteine**

- **Resveratrol and tea extract(EGCG)**

- **Resveratrol and N-Acetyl-Cysteine**
Research with combination of ingredients in CytoQuel®

- **Resveratrol, curcumin, and tea extract (EGCG)**
  - Dominiak K. Et al. Critical need for clinical trials: an example of a pilot human intervention trial of a mixture of natural agents protecting lymphocytes against TNF-alpha induced activation of NF-kB. *Pharm Res.* 2010 June; 27(6)

- **Resveratrol, Curcumin, and EGCG and Tocotrienols**
Research with combination of ingredients in CytoQuel®

- **Curcumin and Resveratrol**

- **Tocotrienols and Curcumin**
  - Steuber N. Et al. Tocotrienol nanoemulsion platform of curcumin elicit elevated apoptosis and augmentation of anti-cancer efficacy against breast and ovarian cancers. *In J of Mol Sc.* 2016 Nov;17(11):1792.