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REPORT

Reverse Mitochondrial Damage

Potent Molecular Energizers for Lifelong Health

By Julius Goepp, MD

Progressive loss of function in the *mitochondria*—the cellular generators responsible for nearly all the body's energy output—speeds aging and death.

Mitochondrial *dysfunction* has been linked to an array of degenerative illnesses, ranging from diabetes and neurological disorders to heart failure.[1,2]

In 2007, a group of researchers reported a **major (but little-known) breakthrough** in our understanding of how mitochondrial dysfunction unfolds—and what can be done to protect yourself against its lethal impact.[3]

They discovered that potentially deadly defects in human mitochondria, including molecular decay and membrane injury, begin to appear and can be detected **nearly a decade before the onset of permanent damage to the DNA.**[3]

More importantly, their analysis revealed that in its initial stages, mitochondrial dysfunction is ***reversible,*** enabling the life and health of cells to be prolonged at the molecular level. The key lies in early interventions to ensure *optimal* mitochondrial function before ***irreversible*** DNA damage occurs.

In this article, we review the latest research on a set of compounds that specifically target and enhance mitochondrial function through multiple modes of action.

THE CELLULAR DEATH SPIRAL

Mitochondria are responsible for converting energy from the food you ingest into usable "currency." Carbohydrates, fats, and proteins are broken down inside your cells into components that enter the cellular powerhouses known as mitochondria. Throughout this cellular journey, these "macronutrients" undergo a complex series of biochemical transformations that generate *adenosine triphosphate* (ATP), the molecular energy currency behind all biological functions. To give you an idea of ATP's lifesustaining importance, your body converts a volume of ATP equal to your entire weight *every day.*

At the core of this energy conversion matrix lies the ***electron transport chain,*** a series of molecules embedded in the inner mitochondrial membrane. It serves as the "power line" through which needed chemical energy is released and transferred into vital ATP.

This energy-intensive process throws off an immense number of electrons within the mitochondria, resulting in constant exposure to **free radicals**—and rendering the mitochondria especially vulnerable to oxidative damage.[4-6]

The result is a cellular *death spiral:* the mitochondria gradually deteriorate, leading to a decrease in vital ATP production and a

deadly increase in free radical generation. Over time, this continuous free-radical onslaught destroys the mitochondria through progressive membrane damage and molecular decay.

As levels of oxidative damage from mitochondrial dysfunction steadily rise with age,[7,8] the body's antioxidant defenses gradually weaken at the same time, accelerating cellular senescence and death.[4,9,10]

Left unchecked, this fatal cycle speeds the general decline in overall function that accompanies aging[4,11] and contributes to the

onset of degenerative disease.[12-15]

COQ10'S REJUVENATING POWER

Coenzyme Q10 (CoQ10) powerfully safeguards mitochondria from age-related decay and death through two principal pathways.

It plays an essential role in the ***electron transport chain,*** facilitating the efficient transfer of electrons into ATP for use in cellular function.[16] CoQ10 resides primarily on the inner membranes of the mitochondria; **95%** of all cellular energy production depends on it.

CoQ10 also acts as a powerful free radical scavenger, neutralizing their lethal action and dramatically reducing oxidative damage. The more available CoQ10 in the mitochondria, the less free radical damage.[16] This is one of the reasons why the highest CoQ10 concentrations are found in the most energy-intensive organs: the brain, heart, liver, and kidneys.[17]

CoQ10 levels in our vital organs, like the heart, steadily rise after birth and peak at about 20 years of age. After that, they undergo a continuous decline.[18] Fortunately, three decades of cutting-edge research have shown us how to restore CoQ10 levels in the mitochondria to slow and even reverse the effects of aging.[19-22]

In pre-clinical models, CoQ10 supplementation protects tissue from lethal DNA damage and increases lifespan.[23] It boosts mitochondrial function and total energy output in heart muscle in aging animals.[24] And in animal models, lifelong CoQ10 supplementation has been shown to decrease oxidative damage in skeletal muscle, increase native antioxidant enzymes, and favorably modify age-related changes in muscular energy metabolism.[25]

Until 2007, the only form of CoQ10 available was *ubiquinone*. Unfortunately, the ubiquinone form ofCoQ10 has limited absorption.[26] Another form of CoQ10, known as ubiquinol, remains up to eight times longer in the blood.[27,28]

The Heart Health Warrior

Dense with mitochondria, the heart requires more energy than any other organ—and the greatest concentration of CoQ10.[29] This is especially true for aging individuals, even those with advanced chronic heart disease. Scores of studies show that chronic heart conditions, including **congestive heart failure** (CHF), are characterized by diminished levels of CoQ10 in heart tissue. Its therapeutic benefit has proven just as profound for these individuals.

In a 2008 study, **standard** CoQ10 supplements failed to improve either CoQ10 levels or cardiac performance in individuals suffering from CHF, while ***ubiquinol*** succeeded on both fronts.[30]

The study involved individuals with advanced CHF. Their hearts pumped less than half as well as normal, with low CoQ10 levels despite taking an average of **450 mg/day** of standard CoQ10. When the same people took ubiquinol (**580 mg/day** on average), their CoQ10 blood levels vaulted into the therapeutic range—and their hearts' pumping action improved by **77%.**

At the outset of this study, every participant suffered from category IV CHF (the most severe form), presenting continuous symptoms—even at rest—with severely limited activity. By the end of the study, the average CHF score had fallen to category II, indicated by mild symptoms (such as slight shortness of breath and/or angina) and minimal limitations during ordinary activity.[31]

CoQ10 supplementation also increases heart muscle ***contractility***—the strength of the heart's squeezing action—enabling the heart to pump more blood more efficiently, even in patients with advanced CHF.[32]

Chronic CoQ10 deficiency has been linked to poor surgical outcomes in elderly patients compared to younger ones.[21,33] By energizing cardiac mitochondria, CoQ10 exerts a powerful effect on cardiac performance in individuals with CHF.

Supplementation with CoQ10 and other antioxidants and heart-energizing nutrients such as L-carnitine and taurine reduces distended heart volume in patients—a vital factor in reducing the risk of bypass surgery.[34]

Following a heart attack, cardiac tissue is at great risk for further injury, including a second attack. In patients recovering from recent heart attacks, just **120 mg** of CoQ10 per day produced remarkable benefits.[35] After one year, only **25%** of supplemented patients suffered a cardiac event, compared with **45%** in the placebo group, and cardiac deaths were significantly fewer compared with placebo. Supplemented patients also had increased high-density lipoprotein (HDL) and dramatically lower measures of oxidative stress.

CoQ10 also benefits people undergoing cardiac surgery, particularly older adults whose outcomes tend to be worse than younger people's, owing to declining mitochondrial function and density in heart tissue.[21]

Treating heart tissue with CoQ10 improves its metabolic stress response and speeds recovery after ischemia (loss of blood flow)—two major concerns after cardiac surgery.[21] Oral CoQ10 therapy for one week before surgery improves mitochondrial energy efficiency and post-operative heart function, while reducing heart muscle damage and shortening hospital stays.[21] A 2008 study also showed significantly fewer arrhythmias (abnormal heart beats), less need for medications to boost cardiac strength, and less need for blood transfusion in patients who received CoQ10 supplementation prior to cardiac surgery, compared to patients who did not receive CoQ10.[36]

WHAT YOU NEED TO KNOW: MITOCHONDRIA HEALTH

- Mitochondria are the cellular organelles that power every energy-requiring bodily process.
- Progressive loss of function in the *mitochondria*—the cellular power generators responsible for nearly all energy output in the body—speeds cell aging and death.
- Researchers recently discovered that signs of age-related mitochondrial damage appear nearly a decade before the onset of ***permanent*** DNA damage.
- They also found that mitochondrial decay and dysfunction are *reversible*.
- A handful of mitochondrial-energizing nutrients have been shown to offer powerful protection from mitochondrial damage and dysfunction.
- CoQ10 speeds mitochondrial electron transport, increases energy production, and protects tissues from mitochondrial decline. ▪ Shilajit, an ancient Indian adaptogen, enhances CoQ10's mitochondrial benefits and supports levels of the active ubiquinol form.
- R-alpha-lipoic acid further supports mitochondrial energy production. ▪ Acetyl-L-carnitine "feeds" energy-releasing molecules to mitochondria, improving their efficiency and preventing damage.

Life Extension Magazine February 2010

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Potent Endothelial Defense

The lining of our blood vessels, or ***endothelium,*** regulates blood flow and pressure, and is easily damaged by oxidative stress and inflammation, which increases the risk of atherosclerosis and erectile dysfunction. CoQ10 powerfully protects endothelial function, an effect that is likely due to its uniquely beneficial effect on mitochondrial function.[37]

One study of the **ubiquinol** form of CoQ10 showed that it protects against hypertension, improves endothelial function, and reduces cardiac enlargement in stroke-prone rats.[38] When humans with endothelial dysfunction took **300 mg/day** of CoQ10 orally for one month, their blood vessels relaxed more readily and they moved more oxygenated blood into tissues compared with placebo recipients.[39]

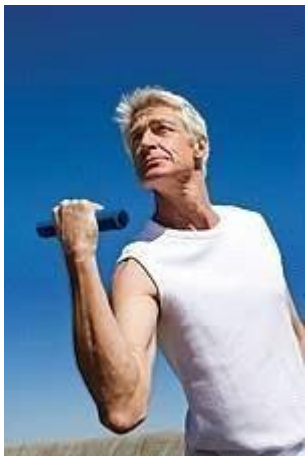
People with type 2 diabetes are at particularly high risk for endothelial dysfunction, and have more heart attacks and strokes as a result.[40] CoQ10 supplementation is especially effective at improving endothelial function in this population.[41] Diabetics (and others) often need to take statin-type lipid-lowering medications to control their cholesterol levels. Unfortunately, these

drugs (also known as HMG Co A reductase inhibitors) are known to deplete CoQ10 and can cause muscle pain that may be related to this depletion.[42] CoQ10 overcomes this problem and has been shown to improve endothelial function in diabetic patients on statins.[43]

Mitochondrial dysfunction is linked to a broad range of degenerative illness, from diabetes andneurological disorders to heart disease.

Muscular Energy Enhancement

Exercise can boost longevity and even increase mitochondrial density in the short term; however, exercise can also *damage* the mitochondria in the long term.[44,45] The high rate of oxygen and electron flow that exercise requires can lead to chronically low ATP levels, which may exert negative effects during vigorous exercise.[46] CoQ10 supplementation can counteract such effects, enhancing the adaptive response of skeletal muscle following exercise.[47]



CoQ10 supplementation before exercise increases muscle CoQ10 levels, reduces muscular oxidant stress, and may increase the amount of time you can exercise until exhaustion.[48] To take one dramatic example, CoQ10 supplementation of 300 mg/day resulted in improved blood markers of exercise-induced muscle injury among elite Japanese Kendo athletes (a form of martial arts) practicing up to five-and-a-half hours per day.[49]

CoQ10 at just **100 mg/day** even enhances performance of normally sedentary men during repeated bouts of exercising.[50] Supplementation of **300 mg/day** enabled adults to increase their velocity on a stationary bike compared with placebo, while reducing fatigue.[51]

CoQ10's remarkable energy-boosting effects can also reduce adverse effects associated with statin therapy, including fatigue, muscle pain, shortness of breath, memory loss, and nerve pain in the extremities.[52] Patients with statin-induced fatigue who stopped the drug and took **240 mg/day** of CoQ10 saw a decrease in fatigue from **84%** to just **15%;** a drop in muscle pain from **64%** to **6%,** and a decline in shortness of breath from **58%** to **12%.** These are all manifestations of restored mitochondrial energy and function—and the study found no adverse consequences from discontinuing the statin drugs.

(You should never abruptly discontinue ***any*** medication without discussing it with your doctor.) ***System-Wide Protection***

CoQ10 also has dramatic benefits in other tissues, particularly in the brain, eyes, and skin.

There's growing recognition of the role of "brain energetics," including mitochondrial health, in causing (or preventing) progressively fatal neurological conditions, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis
(ALS or Lou Gehrig's Disease).[12,53] Animal studies show that CoQ10 supplementation increases brain levels of CoQ10, sustaining the brain's tremendous energy needs. At the same time it reduces brain injury and increases life span in mice with a neurodegenerative disease similar to ALS.[54]

CoQ10 benefits peripheral nerves as well. People with diabetes often succumb to painful diabetic neuropathy and decreased ability to sense pressure, which can lead to disastrous injuries. Studies of diabetic rats with neuropathy show that CoQ10 improved nerve conduction velocity and strength of nerve impulses.[55]

Nerve cells in the eye are faced with enormous energy demands—they must convert light into electrical impulses, while protecting themselves from the damaging effects of both.[56] Researchers now know that mitochondrial health is vital to sustaining the health of cells in the retina, where optical nerves are concentrated.[57] Unfortunately, CoQ10 levels in the retina decline rapidly with age, leaving delicate cells vulnerable.[58]

In combination with acetyl-L-carnitine and omega-3 fatty acids, CoQ10 generated dramatic results in studies of individuals suffering from early age-related macular degeneration. Supplemented patients had a **10-fold lower risk** of worsening over a 12month period, compared with those who received placebo![59] Pre-clinical models suggest that CoQ10 may even protect retinal tissue from the effects of glaucoma.[56]

Our skin shows the most immediate and visible signs of aging. Only recently have we learned how much this has to do with mitochondrial dysfunction in skin cells: skin biopsies from older people show substantially less mitochondrial function than those from younger people.[60]

Increased oxidative damage from diminished mitochondrial function has been shown to trigger inflammation and launch proteindestroying enzymes into action. Over time this leads to a weakening of the delicate matrix of skin tissue, spots, wrinkles, dryness—even cancer.[61] Many studies show that topical CoQ10 treatment inhibits inflammatory cytokines, reduces wrinkling enzyme production, and improves the appearance and radiation-resistance of older skin.[61-63] Boosting CoQ10 through oral supplementation also affords vital protection.[64]

ADVANCED MITOCHONDRIAL THREATS: GLYCATION AND LIPOXIDATION

The chemical reaction of glucose with proteins and fats that occurs over a lifetime produces **advanced glycation endproducts** (AGEs) and **advanced lipoxidation end-products** (ALEs).[104] These deadly molecules cause oxidative and inflammatory damage to mitochondria, hastening mitochondrial dysfunction and aging.[105-109] Specific compounds have been shown to provide targeted mitochondrial defense against glycation and the inflammation it produces.

- **Carnosine** is a nutrient comprised of two amino acids. It's a natural antioxidant and anti-glycation molecule proven to reduce reactive oxygen and nitrogen species resulting from chronic glucose exposure, while also binding to potentially dangerous metal ions (chelation). These features make it attractive as an anti-aging, anti-Alzheimer's agent.[110-112]
- **Luteolin** is a flavonoid with potent anti-inflammatory effects.[113,114] It directly inhibits AGE formation at early, middle, and late stages in their development—more powerfully than standard chemical AGE-inhibitors.[115,116] It also directly counters the sugar-induced mitochondrial damage caused by reduction in a survival protein called Bcl-2.[117]
- **Benfotiamine** is a fat-soluble form of thiamine (vitamin B1). Its higher bioavailability allows it to strongly increase glycation-fighting thiamine levels in blood and tissues in normal people and in people with either type 1 or 2 diabetes.[118120] Benfotiamine powerfully reduces AGE production and damage to vascular endothelial cells under high-glucose conditions.[121,122] It blocks three distinct pathways of sugar-induced tissue damage to protect against retinal damage in diabetes.[123]
- **Pyridoxal -5'-phosphate** (PLP) is the biologically active form of vitamin B6. It is a powerful inhibitor of both protein and fat glycation.[124,125] Glycation reductions by PLP are credited with reducing sugar-induced blood vessel and kidney damage from diabetes.[126,127]

Each of these nutrients works through distinct pathways, acting as a "therapeutic cocktail" that provides maximum protection against glycation-induced toxicity and mitochondrial damage.[128]

MITOCHONDRIAL PROTECTION WITH A POTENT ADAPTOGEN

Long known to Ayurvedic practitioners for its healing power, ***shilajit*** is an organic substance harvested from biomass high in the Himalayas.[65,66] It acts as a powerful ***adaptogen,*** providing broad systemic defense against stress and illness. Cuttingedge scientific analysis has isolated ***humic substances*** as the principal active ingredients that enhance mitochondrial energy flow.[67]

In 2009, a series of landmark studies detailed for the first time how shilajit works on energy metabolism.

Mice subjected to strenuous exercise underwent expected ATP declines in muscle, blood, and brain tissue. **When supplemented with shilajit, ATP loss was sharply reduced.**[68] Other biochemical markers of energy status also dramatically improved in the supplemented animals—including levels of CoQ10, which fell twice as fast in control mice as in supplemented animals. When given in combination, CoQ10 and shilajit displayed a powerful ***synergistic effect.*** Energy parameters such as CoQ10 levels increased significantly more than with either supplement alone.

Further analysis brought some of its key mechanisms of action to light. **Shilajit** contains two primary components, **fulvic acid** and **DBPs** (dibenzo-a-pyrones). **Fulvic acid** independently stimulates mitochondrial energy metabolism, protects mitochondrial membranes from oxidative damage, and helps channel electron-rich **DBPs** into the mitochondria to support the electron transfer chain.[69,70] Fulvic acid works as an electron "shuttle," augmenting CoQ10 to speed electron flow within mitochondria.[71-73]

The DBPs in shilajit serve as electron "reservoirs," replenishing electrons lost by CoQ10 when it donates them to free radicals (thereby neutralizing them).[70,74]

When laboratory mice are supplemented with oral CoQ10 alone, CoQ10 levels rise in heart, liver, and kidney tissue, as might be
expected.[75] When DBPs from shilajit are added to the supplement, CoQ10 levels rise still further—as much as **29%** in the liver.[75]

A recent study suggests that DBPs from shilajit preserve CoQ10 in its superior ***ubiquinol*** form.[75]

Preliminary findings suggest that shilajit protects human tissue from lost energy in the form of ATP, while maximizing benefits from CoQ10, with dramatic improvement in exercise performance.[76] In an as-yet unpublished study, people who took shilajit **200 mg** once daily for 15 days registered **14%** higher post-exercise ATP levels in the blood—equivalent to levels in people who hadn't exercised at all. The average number of steps they took on a standardized dynamic exercise test rose significantly, and their mean fitness scores increased by **15%**—without any intervening exercise training.

In pre-clinical studies, shilajit has been shown to possess a number of additional benefits, allowing it to work in *synergy* with CoQ10 to protect and support mitochondrial health:

- Preliminary unpublished studies showed that shilajit (**250 mg** twice daily for 90 days) lowered fasting **blood sugar** and a measure of **systemic inflammation** called the ESR (erythrocyte sedimentation rate), while increasing hemoglobin levels and platelet counts.[77,78]

- Shilajit protected laboratory rats from developing chemically-induced **diabetes** through its free-radical scavenging properties.[70]

- Shilajit *augmented* learning acquisition and memory retrieval in laboratory rats while reducing manifestations of anxiety during maze experiments.70

- Shilajit reduced levels of the enzyme *acetylcholinesterase* that destroys the vital neurotransmitter **acetylcholine.** This effect may help to prevent or treat Alzheimer's disease by maintaining levels of the neurotransmitter.[70]

- Shilajit increased levels of the neurotransmitter **dopamine** in rat brains, making it an attractive candidate for treatment of Parkinson's disease and other movement disorders.[70]

- In pre-clinical studies, shilajit produced significant increases in the endogenous antioxidants ***superoxide dismutase*** (SOD), ***catalase,*** and ***glutathione peroxidase*** in brain tissue. Increased levels of these enzymes protect vulnerable brain cells against the oxidative damage that leads to brain aging and cognitive decline.[70]

Life Extension Magazine February 2010

REPORT

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A COMPLEMENTARY COENZYME

Lipoic acid is a naturally occurring compound found in mitochondria. Like CoQ10, it is a ***coenzyme*** required for proper function of the mitochondrial energy chain.[4] Lipoic acid directly increases ATP production in mitochondria.[79] Clinical models indicate that lipoic acid may serve as a first-line defense for diseases involving impaired energy utilization, including diabetes and the nerve damage associated with it.[80-82]

R-alpha-lipoic acid is the most bioactive form of lipoic acid—and a powerful activator of mitochondrial energy complexes.[83,84] Studies in aging animals support the use of R-alpha-lipoic acid to improve mitochondrial function, decrease oxidative damage, and increase metabolic rate, all of which otherwise become impaired with aging.[4]

R-alpha-lipoic acid has been proven effective in reducing symptoms of diabetic neuropathy, without significant adverse reactions.[81,85] It also increases nerve conduction velocity in people with diabetic neuropathy, crucial to improved nerve signaling.[86] Experts attribute these effects to diminished fat oxidation in nerve cell membranes and improvements in local blood supply around nerves resulting from improved mitochondrial functioning.[87,88]

R-alpha-lipoic acid displays many protective effects. It reverses the age-related increase in liver cell damage caused by exogenous toxins, helping to protect liver function.[89] It prevents brain cells from becoming depleted of the natural antioxidant *reduced glutathione,* an important intracellular antioxidant in the body. Deficiency of reduced glutathione can predispose people to liver failure, Parkinson's disease, and other neurodegenerative conditions.[90,91] A therapeutic dose of **600 mg/day** even helped relieve migraine attack rates—an observation that may support the theory that migraines may be partially caused by impaired mitochondrial function.[92]

As you might expect of a mitochondrial energy booster, lipoic acid may also play a role in helping to ward off cardiovascular disease. Three months of lipoic acid supplementation provided pain relief to patients with peripheral vascular disease (PVD), extending the time they could walk before pain occurred.93 Combined therapy with acetyl-L-carnitine improved blood vessel relaxation and blood flow, while reducing blood pressure, in patients with coronary artery disease.94 And combined supplementation is a very good idea, as we'll see next.

YOUR MITOCHONDRIAL FAT-BURNER

L-carnitine is a molecule required for helping transport fatty acids into the mitochondria, where they can be burned as fuel. Acetyl-L-carnitine (ALC) is the *form* of carnitine optimally absorbed through oral delivery. It has also been shown to boost mitochondrial health, facilitating fuel delivery to the electron transport chain, where supplements like CoQ10, shilajit, and lipoic acid take over.

Total carnitine levels diminish with age, a decline that may also be accelerated by overeating and diabetes.[95] As with other mitochondrial energy optimizers, ALC supplementation possesses distinct benefits across numerous physiological systems.[96]

A review of clinical studies shows that ALC may slow the natural course of Alzheimer's disease.[97] It has substantially increased Alzheimer's disease patients' responses to drug treatment, from **38%** to **50%** in one study.[98] ALC also protects brain tissue against destructive effects of hypoxia (low oxygen), by supporting cellular metabolism.[99] ALC and lipoic acid supplementation partially restored depleted brain mitochondrial activity in aged rats to that of young adults.[100]

The combination of ALC with lipoic acid improved cognitive function in a mouse model of Alzheimer's disease.[101] ALC alone has exhibited powerful effects, restoring aging animals' cardiac energy metabolism to that of young adults.[102] In combination with lipoic acid, ALC helps maintain heart muscle function in aging animals as well.[103]

SUMMARY

Mitochondrial dysfunction is linked to a broad range of degenerative illness, from diabetes and neurological disorders to heart disease. Researchers have discovered that age-related mitochondrial dysfunction—which can ultimately lead to DNA damage and cell death—may be prevented and even *reversed.* The key lies in early and sustained interventions that support optimal mitochondrial health and function. CoQ10 in its superior form as **ubiquinol** may restore mitochondrial function. The organic

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adaptogen ***shilajit*** acts in synergy with ubiquinol, further enhancing mitochondrial function. R-alpha-lipoic acid and acetylLcarnitine have been shown in clinical studies to provide additional mitochondrial support.

If you have any questions on the scientific content of this article, please call a Life Extension® Health Advisor at 1-8668643027.

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