



HOPE. ENERGY. LIFE.

Supplements and Nutrition

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Supplements

• Overview

- Mitochondrial dysfunction often leads to elevated free radical production, a reduction in aerobic energy provision, and high flux through anaerobic pathways that can increase serum lactate (lower pH) and deplete tissue phosphocreatine¹. Many of the suggested supplements for mitochondrial disease have been based upon the predicted ability to mitigate against these effects and are often given in combination as a “mitochondrial cocktail.”²
- No long-term (> several months), randomized studies have been completed to date and all recommendations are somewhat empiric and must be individualized. In theory, combinations of supplements that target more than one of the consequences of mitochondrial dysfunction should be superior to single agents¹, and some evidence suggests that combination therapies can improve surrogate markers of efficacy, including oxidative stress markers and lactate, and improved mitochondrial function³⁻⁵. Most studies have evaluated coenzyme Q10, creatine monohydrate, riboflavin, vitamin E, vitamin C, α -lipoic acid, and thiamine (Table 1). Until evidence of safety and efficacy is established, patients should avoid the hundreds of other supplements on the market.
- A randomized double-blind, cross-over study using a combination of α -lipoic acid + creatine monohydrate + CoQ10 in proven mitochondrial disease showed decreased levels of lactate and of a marker of oxidative stress³, and another similar combination also found evidence for efficacy *in vitro*⁵.
- A wide variety of other supplements have been advocated for use in mitochondrial cytopathies including: riboflavin (co-factor for complex II), thiamine (co-factor for pyruvate dehydrogenase), vitamin K3 (electron donor), succinate (co-factor for complex II), yet none have been independently evaluated in a randomized clinical trial. Most physicians do not prescribe vitamin K3 anymore as there may be the potential for blood clotting alterations.
- **Coenzyme Q10** is a co-factor involved in electron transfer from complex I and II to complex III of the electron transport chain and can function as an anti-oxidant. There are many studies that have evaluated the potential efficacy of CoQ10 in mitochondrial disease, but the literature is not conclusive due to different formulations (some of which are poorly absorbed), small sample size, and variability in clinical features and outcome variables. The balance of data suggests that CoQ10 is likely to be of benefit in primary, and some secondary, mitochondrial disorders (review see^{1,2,6}).
- **Alpha-lipoic acid** is an anti-oxidant located in the mitochondria with high theoretical potential for use in mitochondrial disease¹, although it has been studied only as part of a combination to date³.
- **Creatine monohydrate** is a guanidino compound that is consumed in meat/fish and produced endogenously. It is involved in temporal and spatial energy buffering in the cell and has anti-oxidant and neuroprotective effects⁷⁻⁹. Animal models of complex I and II deficiency, cerebral ischemia, seizures, and oxidative stress, all show beneficial effects from creatine supplementation⁷⁻¹⁰. Human studies using creatine

monohydrate in isolation have been equivocal: some have reported benefit¹¹⁻¹⁴, others have not^{15, 16}.

- **L-carnitine** is required for the entry of long-chain fatty acids into the mitochondria for β -oxidation. Supplementation is recommended if plasma levels are low, or if patients are taking valproic acid or statins (both relatively contraindicated in mitochondrial disease).
- **Vitamins E and C** are lipid- and water-soluble anti-oxidant vitamins, respectively. Free radicals are produced in excess from complex I and III of the electron transport chain in response to mitochondrial dysfunction and result in oxidative stress. It is important that anti-oxidants be given as redox-couples because each anti-oxidant can become a pro-oxidant. Examples of redox-couples include vitamin E and C, vitamin C and CoQ10. The use of a mitochondrial cocktail avoids the use of single anti-oxidants and reduces the risk that they become pro-oxidants.
- **Dosing Guidelines**
 - Supplements should be introduced in a step-wise fashion and increased slowly to identify and minimize potential intolerances.
 - All supplements can lead to drug interactions with prescription medications. In those people taking concomitant medications, it is important to evaluate drug levels (when possible) after starting a mitochondrial cocktail, especially if there is a change in clinical condition or if a new sign/symptom emerges.
 - With the exception of coenzyme Q10, where there is some evidence that liquid/hydrosoluble formulations are better absorbed and lead to higher blood levels than powder preparations³, for the other components of mitochondrial cocktails there is no credible data to suggest that one formulation is better than any other (Table 1).
 - Targeted formulations have been designed to be more specific for the mitochondria (e.g. MitoQ)¹⁷, and future clinical trials will be important to evaluate their clinical utility.

Nutrition.

- Before starting any diet or dietary supplement, ensure that energy, protein, and micronutrient intake are sufficient. Some patients have increased energy expenditure (e.g. because of fever, rigidity, dystonia) and/or reduced energy intake (e.g. because of low intake due to oro-facial weakness or dyskinesia), or poor absorption (e.g. due to intestinal pseudo-obstruction) that can lead to relative under-nutrition. Identification of deficiencies that may require specific supplementation can be done with blood tests and are most commonly seen for protein (albumin or pre-albumin), folate (RBC folate), vitamin B12 (B12 level), and carnitine (total and free carnitine levels). In our hands we have found B12 deficiency in ~ 13 % of our patients and vitamin D insufficiency in over 80 % of patients. Other deficiencies that we have observed include; zinc, selenium, vitamin A, and vitamin E.
- A multivitamin supplement is safe and may alleviate micronutrient deficiencies. Patients with LHON, NARP, or other mitochondrial disorders with retinal involvement should take a multivitamin with lutein.
- Some patients require a G- or J-tube to safely provide adequate nutrition +/- medications.

- There is no scientific data to support specific macronutrient profiles (ratios of protein, carbohydrate and fat) in mitochondrial disease, but protein needs should at least meet the guidelines set out in the Dietary Reference Intake Tables prepared by the US Department of Agriculture, http://fnic.nal.usda.gov/nal_display/index.php?info_center=4&tax_level=3&tax_subject=256&topic_id=1342&level3_id=5140.
- A ketogenic diet is used in the treatment of refractory seizures and is not contraindicated in mitochondrial disease. Although there may be potential benefits from a ketogenic diet in complex I deficiency ¹⁸, the long-term health risks would preclude its use except in the case of severe refractory seizures.
- Fasting should be avoided and frequent small meals are preferable. If fasting is unavoidable (e.g. for religious reasons), a meal with fat and protein (slow digestion) and complex carbohydrates (slow absorption) should be taken prior to a planned fast.
- Fluid intake is essential during times of increased heat and metabolic stress to avoid heat stroke. Fluid intake should match the environmental demands (more fluid intake in hot/humid conditions). A general rule is to consume or administer adequate fluids to keep the urine color light yellow or clear. Absence of sweating in a warm environment is a serious sign of heat stress and must be dealt with promptly. Guidelines on the recognition of heat stress and heat stroke and prevention can be best obtained through documents designed for sporting events: <http://www.acsm-msse.org/pt/pt-core/template-journal/msse/media/0207.pdf> and <http://www.acsm-msse.org/pt/pt-core/template-journal/msse/media/0307.pdf>. These documents provide general principles on the recognition and treatment of heat stress and heat stroke.

Table 1. Nutraceutical compounds often used with mitochondrial cytopathies

Compound	Dose (mg/kg/d)	Rationale
Coenzyme Q10	3.5 – 15.0 ¹	By-pass complex I defect/anti-oxidant
Creatine monohydrate	100.0 ² (max, 7g/d)	Alternative energy source/neuroprotection
Riboflavin	2.5 – 5.0	By-pass complex I defect
Alpha-lipoic acid	3.5 – 10.0	Anti-oxidant
Vitamin E	5.0 – 10.0 ³	Anti-oxidant
Vitamin C	5.0 – 10.0	Anti-oxidant
L-carnitine	15.0 – 50.0 ⁴	Free fatty acid transport/neuroprotection
Thiamine	2.5 – 5.0	Enhance pyruvate entry into mitochondria

Although most of the above compounds are Generally Regarded As Safe (GRAS), none of the above has been proven to be safe during pregnancy. Since pregnancy is a metabolic stress and the developing fetus may be affected with mitochondrial disease, the risk/benefit ratio is unclear and must be individualized. The doses given are the best estimate from studies and empirical experience and the total daily doses should be divided twice daily. The supplements are best given with food to enhance tolerance. Gastrointestinal upset is the most common side effect (seen in about 5 % of patients with creatine for example). 1 – Higher doses are required for coenzyme Q10 deficiency; 2 – Uptake into the brain may require higher doses or a loading with up to 300 mg/kg/d for 4 weeks to increase levels by ~ 9 %¹⁹ (consequently, using creatine in an acute stroke or seizure situation is totally useless), uptake into muscle can occur after 30 days with the

above dose and 5 days with loading (300 mg/kg/d)²⁰; 3 – maximum daily dose should not exceed 800 mg = IU; 4 – I tend to adjust the dose to get plasma levels into the mid-normal range for the reference laboratory used.

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