

Why Test for Coenzyme Q10?

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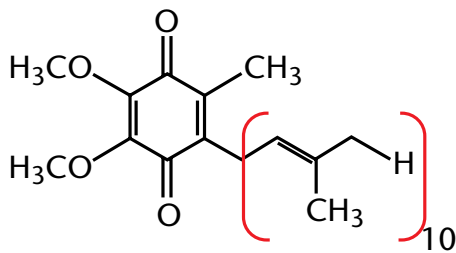
Summary

Humans can display a range of coenzyme Q10 (CoQ10) levels in serum, yet high circulating CoQ10 does not indicate it is sufficient for production of ATP in the mitochondrial electron transport chain. Using statin drugs can interfere with CoQ10 production, compromising cellular energy production. High performance athletes are candidates for testing CoQ10, as well as patients that appear to have mitochondrial dysfunction, neurological or skeletal muscle disorders. Cases of genetic inability to produce adequate CoQ10 have been identified and treated successfully with CoQ10. This article illustrates that measuring both direct and indirect biomarkers of CoQ10 sufficiency in order to appropriately diagnose and treat patients, and to monitor CoQ10 administration, can markedly improve patient outcomes and prevent mitochondrial-related disease.



Metamatrix profiles enable both direct and functional measurement of CoQ10 adequacy for your patient's diagnosis, treatment, and follow-up. In the Organix™ Profile, urinary biomarkers show the functional adequacy of CoQ10 for efficient production of ATP as well as HMG-CoA, the product of the target enzyme of statin drugs upstream of CoQ10 production. The ION™ includes the Organix profile and also directly measures CoQ10 in the patient's serum, while the CardioION™ further measures cholesterol levels (HDL, LDL, and total).

Biochemistry and Physiology



Coenzyme Q10, also called ubiquinone (from ubiquitous), is a quinone with an isoprenoid side chain, widely distributed in most cells. Research has identified CoQ10 as a conditionally essential nutrient. It is found in significant amounts in all nutrient-dense foods. Plants contain a slightly different compound that may serve the electron transport function in animals, though with lower efficiency.

The primary function of CoQ10 is shuttling electrons in the mitochondrial inner membrane. This pathway is frequently referred to as the electron transport or oxidative phosphorylation part of the central energy pathway. As shown in Figure 1, the electrons are received directly from succinate and choline or indirectly from several other substrates such as pyruvate, Acyl-CoA, and alpha-ketoglutarate. The pathway consists of complexes I to V. Complexes I - III are CoQ10 dependent.

CoQ10 moves from one electron carrier complex to the other to ultimately deliver electrons to oxygen, one at a time, in a never-ending cycle of oxidation and reduction. The electrons are delivered one at a time, but the pathway is designed so that they leave in pairs to form ATP and H₂O (Figure 1). If CoQ10 availability is not adequate the electrons will not be able to travel in pairs, and single electrons will take another less desirable pathway that can lead to superoxide production. The pathway operating optimally is critical for the fundamental energy generation that powers all cell functions.

Clinical Importance of CoQ10

Mitochondrial Myopathies. In accordance with its most well known role in mitochondrial function¹, CoQ10 has been shown to improve ATP synthetic capacity in patients with disorders of oxidative phosphorylation.² Symptoms associated with mitochondrial dysfunction include skeletal muscle weakness, exercise intolerance, myalgia, cramps, and even weak extraocular muscles.³ The benefit of CoQ10 administration has been implicated in neurological disorders such as Alzheimer, Parkinson⁴, and Huntington diseases.⁵

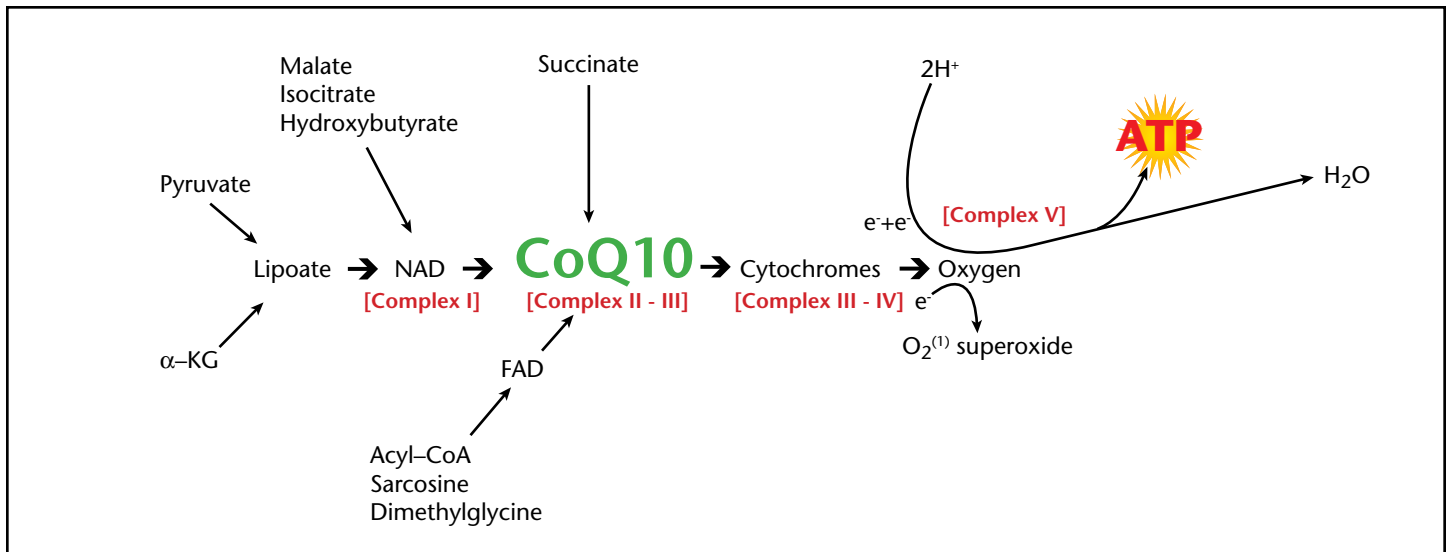


Figure 1. CoQ10 is a major component in electron transfer for ATP production in cellular respiration. Functional markers of CoQ10 are succinate, malate, fumarate, and hydroxymethylglutarate. Other Krebs Cycle intermediates (isocitrate, hydroxybutyrate, alpha-ketoglutarate) are listed here because inadequate CoQ10 can cause accumulation of these compounds in urine in addition.

Patients with mitochondrial encephalomyopathy due to electron transport complex I and IV deficiencies show improved mitochondrial function and an increased capacity for fat metabolism when supplemented with 150 mg/d of CoQ10.⁶ Lactate and pyruvate elevations are reduced in patients with mitochondrial myopathy when they are given daily oral doses of 120 mg of CoQ10.⁷ In a more recent case described as primary deficiency of CoQ10, an 11.5 year old male displayed insidious onset of exercise intolerance and proximal muscle weakness with constitutional fatigue, weight loss, and muscle cramps in his lower extremities. Abnormalities in organic acids and respiratory chain enzymes normalized when CoQ10 was supplemented at 300 mg/d.⁸

One study attributes, “progressive muscle weakness, abnormal fatigability, and central nervous system dysfunction since early childhood,” to a deficiency of CoQ10 in muscle mitochondria. Specifically, complexes I-III and II-III (both dependent on CoQ10) were abnormally low compared to other CoQ10-independent complexes in the respiratory chain.⁹ CoQ10 relieved symptoms of diabetic amyotrophy in a 71 year-old male¹⁰ and a patient with mitochondrial myopathy was completely recovered with CoQ10.⁸

Cardiovascular Disease. The heart, which has the largest, most critical energy demand, and thus the greatest concentration of mitochondria, will show effects of insufficiency of the coenzyme.¹¹ Preoperative oral CoQ10 therapy (300 mg/d) in patients undergoing cardiac surgery increased myocardial mitochondrial CoQ10 levels, improved mitochondrial efficiency and increased myocardial tolerance to in vitro hypoxia-reoxygenation stress. Average serum CoQ10 in this experiment for the control and supplemented groups were 0.4 and 1.6 mcg/mg protein, respectively.¹² Endurance exercised rats showed increases of CoQ10 in heart and skeletal muscle out of proportion with the changes in other electron transport system components, indicating a direct role of the coenzyme in regulation of mitochondrial capacity for forming ATP.¹³

Antioxidant. The antioxidant role of CoQ10, perhaps independent of its function in mitochondrial electron transport,¹⁴⁻¹⁶ has been implicated as one mechanism behind the benefit of CoQ10 administration. CoQ10 administration in 22 humans showed increased levels of reduced CoQ10 in plasma and decreased lipid peroxidation (measured as TBARS).¹⁷ CoQ10 has been shown to slow the progression of clinical symptoms observed in patients with Friedreich’s ataxia, a pathology believed to involve mitochondrial function and increased oxidative stress.¹⁸ An insufficiency of CoQ10 leads to oxidative stress and thus to a long list of disorders, including aging.

Some have suggested that CoQ10 provides protection from toxicity during chemotherapy.¹⁹ Case studies and small studies show beneficial and sometimes curative effects of CoQ10 administration yet large studies do not always mirror those results.²⁰ One reason large studies may not show clinically significant improvement upon CoQ10 treatment is because subjects may be replete in CoQ10 at the initiation of the study.

Statin Effect on CoQ10. CoQ10 synthesis is dependent on the availability of hydroxymethylglutarate (HMG). Thus, if HMG is low it will slow the rate of CoQ10 synthesis. Statin drugs block the conversion of HMG to cholesterol and to CoQ10. HMG accumulates and spills into urine at abnormally high levels that signals reduced CoQ10 biosynthesis (Table 1). Impairment of the synthetic pathway does not necessarily mean functional impairment. While statin drugs are known to reduce endogenous CoQ10 synthesis, routine CoQ10 administration to patients using statin drugs has not yet been completely accepted.²¹ Therefore, it is highly recommended to measure the patient's CoQ10 levels and functional markers before and during administration.

Why Test Your Patient's CoQ10 ?

With the breadth of literature suggesting benefits of CoQ10 supplementation, one might advise all patients to take CoQ10. One author states, however, that administration of CoQ10 to all patients on statin therapy is not recommended while certain groups might benefit from supplementation.²¹

Humans can have widely varying levels of circulating CoQ10 and functional need of CoQ10. Measuring patient levels of CoQ10 not only helps the clinician determine if CoQ10 deficiency is a cause of the patient's complaints, but may also tell the clinician whether the patient would be a "responder" to supplementation with CoQ10. Further, some humans endogenously produce high amounts of CoQ10 and if functional markers demonstrate adequacy, such a patient would not need CoQ10 administration.

Clinical Interpretation of Your Patient's CoQ10 Results. Metamatrix profiles (Organix™, ION™, and CardioION™) enable both direct and functional measurement of CoQ10 adequacy for your patient's diagnosis, treatment, and follow-up. The clinical interpretation of abnormal serum CoQ10 levels may be enhanced by simultaneous measurement of markers that monitor its biosynthetic and functional roles.¹¹

Reduced endogenous production of CoQ10 does not necessarily mean functional impairment. A functional impairment at the level of mitochondrial CoQ10 electron transfer will also affect succinate, malate, fumarate and pyruvate, which are the energy pathway intermediates (see Figure 1 and 2). CoQ10 deficiency causes elevation of these intermediates (Table 1). The direct transfer of electrons from succinate to the flavin mononucleotide (FMN) reductase enzyme in the electron transport system is slowed when the electron shuttle action of CoQ10 is inadequate to meet demands.

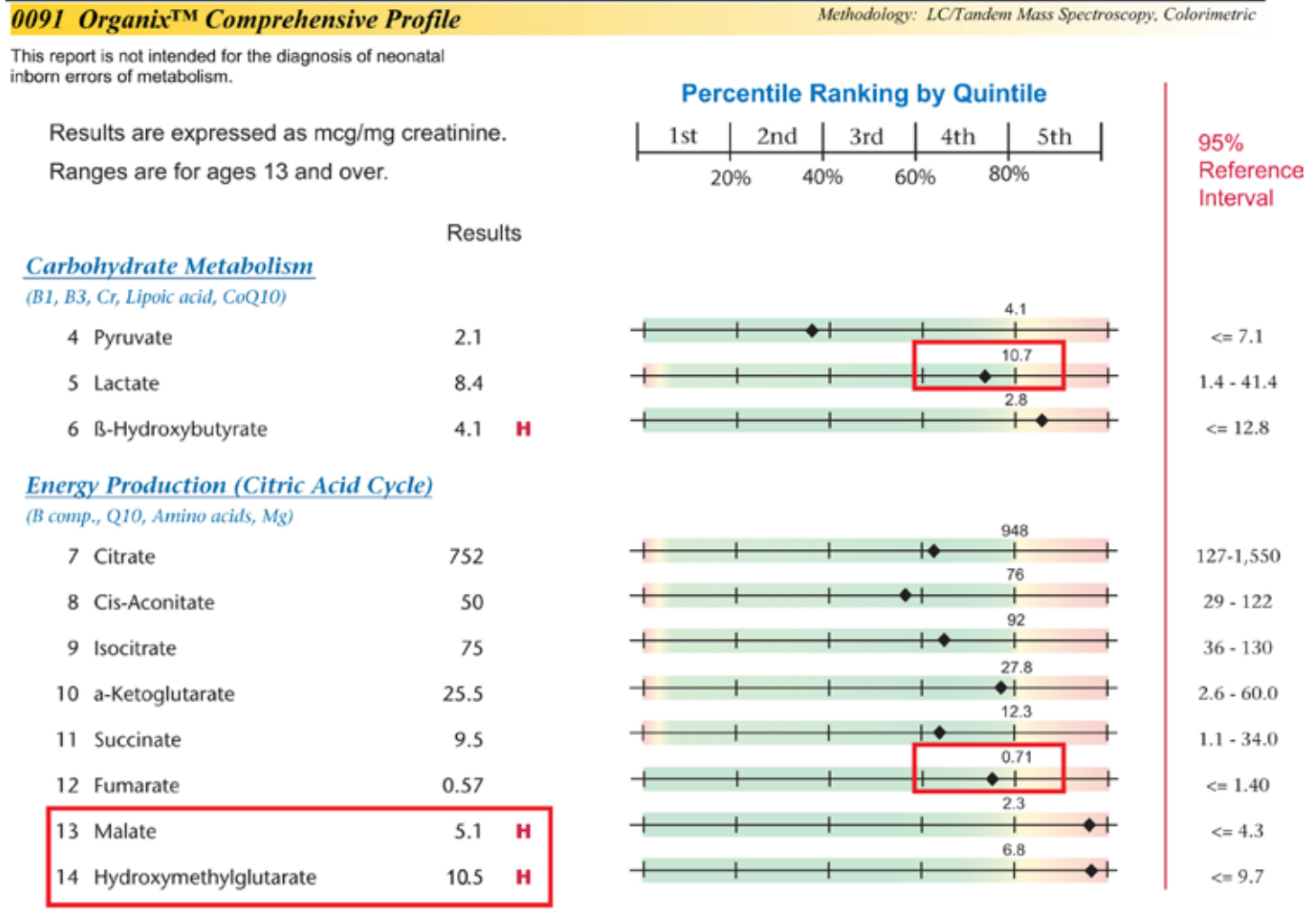
Urinary markers of CoQ10 are included in the Organix, ION, and CardioION Profiles. Serum CoQ10 is measured in the ION and CardioION Profiles. The CardioION Profile additionally measures cholesterol.

TABLE 1. TESTS FOR COQ10 DEFICIENCY

Test	Abnormality	Indication
CoQ10, serum	Low	Sign of depletion of tissue CoQ10
Hydroxymethylglutarate, urine	Low	Metabolic block before HMG
	High	Metabolic block after HMG
Lactate, Succinate, Fumarate, Malate and other Krebs Cycle intermediates, urine	High	Functional insufficiency to meet energy pathway demands

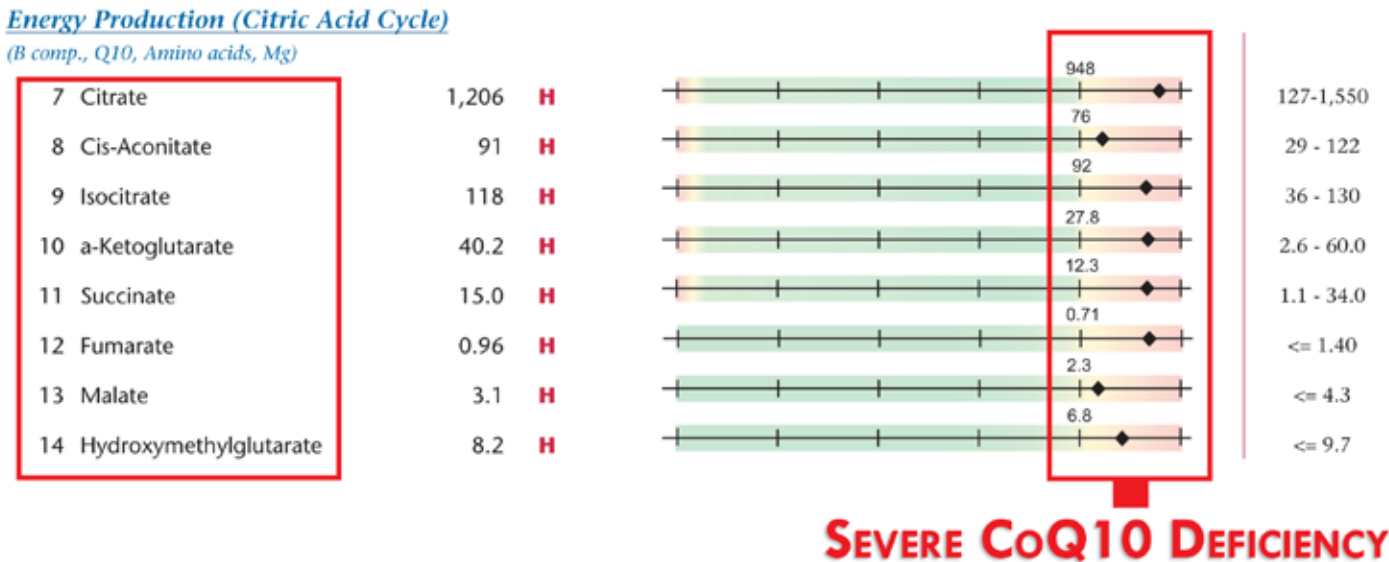
Figure 2 shows the organic acid results for a 31 year old female measured by LC/MS-MS. She was presenting with multiple sclerosis (MS) and had an episode of optic neuritis, from which she still had poor vision. Of the functional markers for CoQ10 adequacy, malate (5.1 mcg/mg creatinine) and hydroxymethylglutarate (10.5 mcg/mg creatinine) are both over the 95% reference interval, indicating clinically significant need of CoQ10 supplementation. Lactate and fumarate are high-normal approaching the 80% cutoff.

Figure 2. Test results for a patient with MS and optic neuritis with dramatic elevation in functional markers of CoQ10.



In patients with mitochondrial dysfunction due to CoQ10 need, not only will the markers for CoQ10 (succinate, fumarate, malate, and hydroxymethylglutarate) elevate, but all of the compounds in the Krebs Cycle will elevate because electrons generated in the Krebs Cycle cannot continue into the electron transport chain to make ATP (Figure 3).

Figure 3. Dramatic need of CoQ10 which elevates all of Krebs Cycle intermediates.



There are multiple reasons for which circulating CoQ10 can be affected: use of prescription medication, poor digestion and absorption of dietary CoQ10, genetic reasons for up-regulated or down-regulated biosynthesis of CoQ10, compromised function of organs rich in mitochondria, or increased demand for ATP production such as in the case of a high performance athlete. While CoQ10 has been shown to improve a variety of clinical conditions, it may not be indicated in all patients. Testing can identify patients that are candidates for CoQ10 supplementation and help to optimize dosing by establishing the point at which a patient is replete and when dosing can be reduced. Therefore, it is important to evaluate CoQ10 production and functional need with laboratory tests as an aid in the treatment and prevention of disease.

See the desk reference book, *Laboratory Evaluations in Molecular Medicine* by Bralley and Lord, for more detailed descriptions of the science behind the Organix™, ION™, and CardioION™ profiles. For a full review of the Organix profile please see Metamatrix Organix Powerpoint at <http://www.metamatrix.com/docs/OrganixOnlineShow.pps>.

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