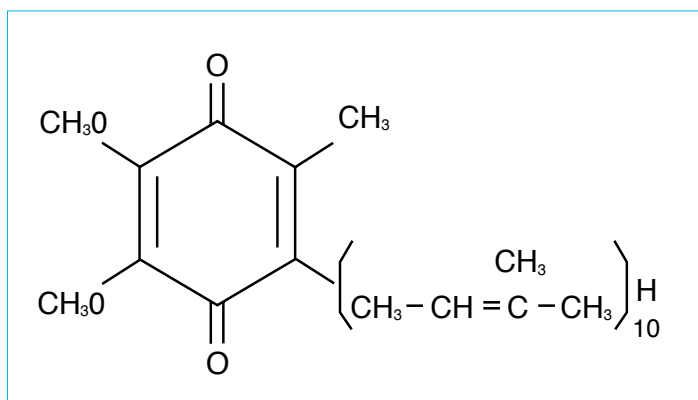




## Coenzyme Q10

### Introduction

Coenzyme Q10 (CoQ10) is a compound found naturally in virtually every cell in the human body. Because of its ubiquitous presence in nature and its quinone structure (similar to that of vitamin K), CoQ10 is also known as ubiquinone. CoQ10 is a fat-soluble substance whose primary role is as a vital intermediate of the electron transport system in the mitochondria. Adequate amounts of CoQ10 are necessary for cellular respiration and ATP production. CoQ10 also functions as an intercellular antioxidant. True deficiency states are rare but often present with severe health consequences. Numerous disease processes, linked to low levels of CoQ10, can benefit from CoQ10 supplementation including cardiovascular disease, Parkinson's disease, muscular dystrophy, breast and other cancers, diabetes mellitus, male infertility, acquired immunodeficiency syndrome (AIDS), asthma, thyroid disorders, and periodontal disease.



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### Biochemistry

Coenzyme Q10 is synthesized intracellularly in the human body using tyrosine as the fundamental building block. This first step requires pyridoxal 5'-phosphate (vitamin B6) as a cofactor, so adequate vitamin B6 nutrition is essential for CoQ10 biosynthesis.<sup>1</sup> Certain situations can disrupt the body's ability to produce enough CoQ10 to meet requirements. Cells and tissues that are metabolically active have the highest CoQ10 requirements (such as the heart, immune system, and gingiva) and as such are most susceptible to CoQ10 deficiency.

### Deficiency States and Symptoms

Tissue deficiencies or subnormal serum levels of CoQ10 have been reported in a wide range of medical conditions, including cardiovascular disease and neuromuscular disease,<sup>2,3</sup> hypertension,<sup>4</sup> periodontal disease,<sup>5</sup> asthma,<sup>6</sup> hyperthyroidism,<sup>7</sup> male infertility,<sup>8</sup> and AIDS.<sup>9</sup> CoQ10 levels decline with advancing age, and this decline might contribute in part to some of the manifestations of aging.

A CoQ10 deficiency could result from: (1) impaired CoQ10 synthesis due to nutritional deficiencies (such as vitamin B6 deficiency), (2) a genetic or acquired defect in CoQ10 synthesis or utilization, or (3) increased tissue needs resulting from a particular illness.<sup>10,11</sup> Clinical presentations of severe CoQ10 deficiency include encephalomyopathy, severe infantile multisystemic disease, cerebellar ataxia, Leigh syndrome with growth retardation, and isolated myopathy.<sup>12</sup> Since oral administration of CoQ10 can increase tissue levels of the nutrient, it is possible to correct CoQ10 deficiency and is particularly essential in the life-threatening infantile encephalopathy.<sup>10,11</sup>

### Pharmacokinetics

CoQ10 is absorbed from the small intestine, passes into the lymphatics, and finally to the blood and tissues. Research on exogenous CoQ10 absorption and bioavailability varies greatly depending on the type of CoQ10 preparation studied. Some studies conclude CoQ10 is well-absorbed by oral supplementation as evidenced by significant increases (168-178%) in serum CoQ10 levels after supplementation.<sup>13,14</sup> In one study, 24 healthy subjects with baseline plasma CoQ10 levels of 0.50-0.52 µg/mL were divided into groups of six and given one of four different

CoQ10 preparations. Three weeks of supplementation at 120 mg daily resulted in plasma CoQ10 values between 1.37 and 3.31  $\mu\text{g}/\text{mL}$ , depending on formulation used.<sup>15</sup> Other research cites slow ( $T_{\text{max}}=6$  hours) and limited absorption due to CoQ10's lipophilic nature and large molecular weight.<sup>16</sup>

While some studies have explored single-dose pharmacokinetics, others have examined the effects of CoQ10 administration for several weeks.<sup>17</sup> A study on intestinal absorption of 30 mg CoQ10 administered in a meal or as powder in capsules to healthy subjects found no significant difference in absorption for these two routes of administration.<sup>13</sup> Although not all research is in agreement, the general consensus is that slightly better absorption is achieved with oil-based forms of CoQ10.<sup>17,18</sup>

## Mechanism of Action

The primary role of CoQ10 is as a vital intermediate of the electron transport system in the mitochondria. Adequate amounts of CoQ10 are necessary for cellular respiration and ATP production. Due to its involvement in ATP synthesis, CoQ10 affects the function of all cells in the body, making it essential for the health of all tissues and organs. CoQ10 also functions as an intercellular antioxidant at the mitochondrial level, perhaps accounting for its benefit in neurodegenerative diseases,<sup>19</sup> male infertility,<sup>20</sup> and periodontal disease.<sup>21</sup>

## Clinical Indications

### Cardiovascular Disease

Numerous studies have investigated the benefit of CoQ10 supplementation for improving cardiovascular function via enhanced energy production, improved contractility of cardiac muscle, and its potent antioxidant activity – particularly prevention of LDL oxidation. In 1994 Langsjoen et al published a study summarizing eight years of research on the usefulness of CoQ10 in clinical cardiology. This summary involved 424 patients with various forms of cardiovascular disease supplemented with oral CoQ10 at daily doses of 75-600 mg (average=242 mg) in addition to their conventional medical regimen. Patients were followed for an average of 17.8 months and clinical response was evaluated according to the New York Heart Association (NYHA) functional scale; medication dependency was

also recorded. Fifty-eight percent of patients improved by one NYHA class, 28 percent by two classes, and 1.2 percent by three NYHA classes. In addition, 43 percent of patients stopped between one and three medications, with no side effects reported.<sup>22</sup> Since this study, numerous other studies have demonstrated the benefit of CoQ10 supplementation for various cardiovascular conditions.

### All-cause Chronic Heart Failure (Cardiomyopathy, Congestive Heart Failure, etc.)

Research has shown CoQ10 levels are depleted in both serum and myocardial tissue samples of patients with chronic heart failure.<sup>23,24</sup> Two important meta-analyses reported significant benefit of CoQ10 on heart failure from various causes. In the earlier report, analysis of research published from 1985-2000 yielded 13 double-blind, placebo-controlled trials with a total of 988 patients. In 10 of the 13 trials, significant improvement was observed in clinical and/or hemodynamic parameters or improved exercise tolerance in patients given adjunctive CoQ10 at doses from 60-200 mg daily.<sup>25</sup>

A second meta-analysis covering a larger time span (1966-2005) investigated the impact of CoQ10 on systolic function in patients with chronic heart failure. Eleven randomized, controlled trials of over 300 patients with chronic heart failure were included. Ten studies evaluated ejection fraction and two also evaluated cardiac output. CoQ10 dosages ranged from 60-200 mg daily and treatment periods ranged from 1-6 months. A statistically significant net improvement in ejection fraction of 3.7 percent was observed, while a more profound effect (6.7%) was noted in those patients not taking angiotensin-converting enzyme inhibitors. Statistically significant improvements in cardiac output and stroke index were also observed in patients taking CoQ10 compared to placebo.<sup>26</sup>

Dilated cardiomyopathy is a form of cardiac muscle disease characterized by ventricular dilation, contractile dysfunction, and eventual congestive heart failure.<sup>27</sup> Cardiomyopathy has been associated with decreased CoQ10 in myocardial tissue and endomyocardial biopsies reveal lower CoQ10 levels correlate with increased disease severity.<sup>24</sup> A study of 88 patients with a diagnosis of idiopathic dilated cardiomyopathy and



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stable chronic congestive heart failure demonstrated 100 mg CoQ10 daily for six months resulted in improved ejection fractions, cardiac output, and improvement in NYHA classification. Of the 88 patients, 75-85 percent had statistically significant improvements in at least two of these parameters. The greatest improvements were noted in patients with the lowest ejection fraction at baseline. NYHA classification also improved by 1-3 classes in 83 percent of patients studied.<sup>28</sup> Employing the same dosage, a longer study (six years) by the same authors investigated the efficacy of CoQ10 in 126 men and women with idiopathic dilated cardiomyopathy (NYHA class III or IV). Within three months, 71 percent of subjects demonstrated significant improvement in ejection fraction and within six months that number increased to 87 percent. Improvements in NYHA class were also noted in 87 percent of patients.<sup>29</sup>

### Dyslipidemia and Statin Drugs

Elevated cholesterol and the associated dyslipidemia are commonly treated with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibiting drugs ("statins"). Because both cholesterol and CoQ10 synthesis depend on HMG-CoA reductase, both can be blocked. Depletion in CoQ10 may account for the statin-induced myopathies observed in some patients, the most serious of which is rhabdomyolysis. From 1990-2004, 13 controlled trials demonstrated significant CoQ10 depletion secondary to statin therapy.<sup>30</sup> Results demonstrated a range of 19-<sup>31</sup> to 54-<sup>32</sup> percent decrease in basal levels of CoQ10 for patients on statin therapy. Consequently, supplementing with CoQ10 is highly recommended to prevent the myopathic side effects associated with the statin drugs.

### Hypertension

Although the mechanism behind CoQ10's antihypertensive effect is not conclusive, it is likely attributed to its ability to induce vasodilation via decreased peripheral resistance in the vasculature.<sup>33</sup> Another hypothesis is that CoQ10's antioxidant properties result in quenching of free radicals that cause inactivation of endothelium-derived relaxing factor and/or fibrosis of arteriole smooth muscle.<sup>34</sup>

A recent meta-analysis of clinical trials investigating the use of CoQ10 for hypertension assessed overall efficacy, consistency of therapeutic benefit, and side effects. Twelve trials conducted since 1975 included a total of 362 hypertensive individuals, lasted from 8-12 weeks, and examined daily CoQ10 doses of 100-120 mg. CoQ10 reduced systolic blood pressure by as much as 17 mmHg and diastolic blood pressure by up to 10 mmHg, without significant side effects. Blood pressure reduction was noted in all 12 trials, regardless of whether CoQ10 was given alone or as an adjunct to standard antihypertensive medication.<sup>35</sup>

### Other Cardiovascular Diseases

Other cardiovascular conditions that may benefit from CoQ10 supplementation include angina,<sup>36,37</sup> acute myocardial infarction,<sup>38</sup> arrhythmias,<sup>39</sup> protection during cardiac surgery,<sup>40,41</sup> and mitral valve prolapse.<sup>42</sup>

### Neurological Conditions

#### Parkinson's Disease

Research suggests CoQ10 may play a role in the cellular dysfunction found in Parkinson's disease (PD), providing a protective agent for Parkinsonian patients.<sup>43</sup> Significantly reduced levels of CoQ10 have been observed in blood and platelet mitochondria,<sup>44</sup> and plasma<sup>45</sup> of PD patients. Since 1998 at least four clinical trials on the efficacy of CoQ10 in PD have been conducted and can be divided into two categories – trials in symptomatic patients on Parkinson's medication and trials in patients with early PD, not yet requiring medication.

Three trials studied CoQ10 in PD patients receiving standard medication (e.g., levodopa, selegiline, etc.). CoQ10 dosages ranged from 380-1,500 mg daily and trial duration was from 1-6 months. Shults et al supplemented 400-800 mg CoQ10 daily for one month and reported no significant improvement in the motor skills portion of the Unified Parkinson Disease Rating Scale (UPDRS) when comparing baseline to last visit assessment.<sup>46</sup> By contrast, Horstink et al supplemented higher doses (1,000-1,500 mg daily) for six months and reported "minor" clinical improvement reflected by slight decreases in total UPDRS scores in treated subjects.<sup>47</sup> The third trial, supplementing 380 mg CoQ10 daily for one month, reported a significant reduction in UPDRS and Farnsworth-Munsell 100 Hue (FMH)



scores compared to placebo.<sup>48</sup> All three trials were small (12-15 treated patients each), but results seem to indicate a positive effect, warranting larger double-blind, placebo-controlled trials.

A pilot trial aimed at determining the most effective dose of CoQ10 for PD used higher doses in combination with 1,200 IU vitamin E in 17 PD patients. Subjects were supplemented with escalating doses of 1,200, 1,800, 2,400, and 3,000 mg CoQ10 daily and plasma levels were measured with each dosage. The plasma level reached a plateau at 2,400 mg daily, suggesting this may be the maximum effective daily dose for treating PD.<sup>49</sup>

In a multicenter, randomized, double-blind, placebo-controlled Phase II trial of untreated early PD, 80 subjects received 300, 600, or 1,200 mg CoQ10 combined with 300 IU vitamin E daily as a fat-soluble carrier. Control subjects received a placebo also containing 300 IU vitamin E. Subjects were evaluated at baseline and after 1, 4, 8, 12, and 16 months. Individuals receiving the highest dose demonstrated the most improvement in UPDRS scores compared to placebo, while evaluation for degree of independence showed significant benefit for those receiving CoQ10 in general. In addition, platelet mitochondrial activity of complexes I-III was significantly increased in patients receiving CoQ10 compared to placebo.<sup>50</sup>

### Huntington's Disease

Huntington's disease (HD) is a progressive neurodegenerative disease characterized by abnormalities in mitochondrial morphology and activity. Researchers in the Huntington's Study Group at Rochester University, New York, conducted a multicenter, randomized, double-blind, 30-month trial comparing the benefit of 600 mg CoQ10 to 600 mg remacemide (an anti-excitatory drug used to treat HD) or placebo in 347 early HD patients. Although a trend toward slowed worsening of total functional capacity was reported in the CoQ10 group, results did not reach statistical significance.<sup>51</sup>

### Mitochondrial Disorders

Five mitochondrial enzyme complexes produce the majority of cellular energy (ATP). Because CoQ10 is a cofactor for complexes I-III, a deficiency results in

a progressive decrease in mitochondrial energy production and a vast array of mitochondrial disorders that can occur at any time in life. Mitochondrial myopathies, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) are due to genetic mutations and can be severe in clinical presentation. Numerous case reports and small, open-label studies describe mitochondrial diseases of varying severity that have responded to CoQ10 supplementation, typically in dosages from 30-300 mg daily.<sup>52-56</sup>

Double-blind clinical trials have also been conducted. Two short-term (three-month) trials investigated the effect of 100 mg CoQ10 daily on various muscular dystrophies (n=12) and neurogenic atrophies (n=15). Although slight improvements in cardiac function and physical performance were noted compared to placebo, the authors suggested the 100-mg dosage may have been too low to provide significant improvement.<sup>57</sup> Another three-month trial included eight patients with mitochondrial encephalomyopathies supplemented with 160 mg CoQ10 daily. Although the researchers reported a trend toward improved muscle endurance, less fatigue during daily duties, and decreased serum lactate and pyruvate levels, only the muscle endurance results reached statistical significance. The study authors hypothesized the dosage was too low to provide significant benefit.<sup>58</sup> In the longest double-blind clinical trial (six months), 44 patients with mitochondrial myopathies from multiple centers were supplemented with 2 mg/kg CoQ10 daily (approximately 165 mg for a 180-pound adult). Sixteen of 24 patients experienced at least a 25-percent decrease in post-exercise lactate levels and were selected as "responders" to continue the study. After a further three months at the same dose, no significant differences were noted between the responder and placebo groups. The reason for lack of long-term therapeutic effect in the responders was unclear; however, it may be attributed to the relatively low dose and short duration of the study.<sup>59</sup> Overall, it appears larger CoQ10 dosages are indicated for mitochondrial disorders.

### Cancer

Decreased levels of CoQ10 have been found in plasma of women with breast cancer and in cancerous breast tissue, and low levels correlated with a worse prognosis.<sup>10,11</sup> Case reports demonstrated 390 mg



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CoQ10 daily resulted in tumor regression and disappearance of previously diagnosed metastasis. One to three years later, depending on the case, metastases had not reappeared.<sup>60,61</sup>

In 117 melanoma patients without metastasis, plasma CoQ10 levels were significantly lower than in control subjects and were associated with primary tumor thickness, with the highest CoQ10 levels associated with thinner tumors. In addition, patients who developed metastases had lower CoQ10 levels than those who did not, and subjects with lower baseline CoQ10 levels had shorter disease-free intervals.<sup>62</sup>

Low plasma levels of CoQ10 have been demonstrated in cervical intraepithelial neoplasia and cervical cancer.<sup>63</sup>

Mechanisms for CoQ10's benefit for cancer may include immune system enhancement and antioxidant activity. CoQ10 can be depleted by the use of the chemotherapeutic drug doxorubicin (Adriamycin®), resulting in cardiotoxicity if a high enough cumulative dose is achieved. Supplemental CoQ10 (100-200 mg/day) can prevent cardiac damage, as well as diarrhea and stomatitis that are caused by this agent, without decreasing its chemotherapeutic effectiveness.<sup>64-66</sup> A systematic review of controlled trials in cancer patients revealed CoQ10 provides protection against cardiotoxicity and liver toxicity in patients receiving anthracycline chemotherapy drugs, such as doxorubicin.<sup>67</sup>

### Diabetes

The electron-transport chain is integrally involved in carbohydrate metabolism. Serum CoQ10 levels in type 2 diabetic patients are often decreased and may be associated with subclinical diabetic cardiomyopathy, reversible by CoQ10 supplementation.<sup>68</sup> In three separate randomized, double-blind clinical trials conducted by the same group of researchers, a total of 194 dyslipidemic type 2 diabetic patients received 200 mg CoQ10 or placebo daily for 12 weeks. One study also compared CoQ10 stand-alone treatment to a CoQ10-fenofibrate combination and to fenofibrate (a lipid-lowering medication) alone. Primary outcomes were endothelial function of the brachial artery,<sup>69</sup> blood pressure,<sup>70</sup> glycemic control,<sup>70</sup> and forearm microcirculatory function.<sup>71</sup> CoQ10 supplementation in this population raised plasma CoQ10 levels, improved endothelial func-

tion in the brachial artery, significantly decreased both systolic and diastolic blood pressure, decreased glycosylated hemoglobin (HbA1C), and in combination with fenofibrate markedly improved both endothelial and non-endothelial forearm vasodilation.<sup>69-71</sup>

### Male Infertility

Mancini et al demonstrated high levels of CoQ10 in human seminal fluid that correlate positively with sperm count and motility. In subjects with varicocele, however, there appears to be no correlation between CoQ10 concentrations and sperm motility.<sup>72</sup> Research has shown CoQ10 given to individuals with idiopathic decreased sperm motility (asthenozoospermia) raises CoQ10 levels in both seminal plasma and sperm cells.<sup>73</sup> In an open, uncontrolled pilot study, 22 subjects with asthenozoospermia were treated with 200 mg CoQ10 daily for six months, resulting in significant increases in CoQ10 levels in seminal plasma and sperm cells and improved sperm motility compared to baseline values.<sup>74</sup>

### HIV/AIDS

Because CoQ10 enhances phagocytic activity of macrophages and increases granulocyte proliferation,<sup>75</sup> CoQ10 supplementation may be of benefit in these patients. CoQ10's antioxidant activity may also help prevent AIDS-related diseases such as cardiomyopathy<sup>76</sup> and lipodystrophy<sup>77</sup> that can be caused by oxidative stress. Blood levels of CoQ10 are lower in AIDS patients and supplementation with 200 mg/day has been shown to increase T4/T8 ratios in these individuals.<sup>78</sup> In a randomized, double-blind, placebo-controlled pilot study, 25 HIV patients with lipodystrophy, peripheral neuropathy, or no symptoms were given 200 mg CoQ10 daily for three months; 10 subjects received placebo. Ninety percent of patients receiving CoQ10 therapy reported an improved sense of well-being and, in the lipodystrophy arm, an average weight gain of 3 kg was observed, compared to 0.2 kg in the placebo group. Three of five subjects with peripheral neuropathy, however, experienced a worsening of symptoms.<sup>77</sup>

### Asthma

Patients with asthma demonstrate decreased plasma and whole blood CoQ10 compared to healthy subjects. It is theorized that low CoQ10 concentrations

may create oxidative stress and contribute to chronic mucosal inflammation.<sup>6</sup> In an open, randomized, crossover trial of 41 bronchial asthma patients, 120 mg CoQ10, in combination with 400 mg vitamin E and 250 mg vitamin C, was administered to asthma patients along with standard anti-asthma therapy (inhaled corticosteroids; beta agonists) for a total of 32 weeks. Patients taking corticosteroids demonstrated decreased plasma CoQ10 levels that may contribute to oxidative stress. Decreased use of corticosteroids was observed when subjects took the antioxidant combination.<sup>79</sup>

### **Thyroid Disorders**

Two studies have documented decreased levels of CoQ10 in plasma<sup>7</sup> and thyroid tissue<sup>80</sup> of individuals with certain forms of hyperthyroidism. In Grave's disease, excessive thyroid hormone stimulation and subsequent activation of mitochondrial function may result in subnormal CoQ10 concentrations.<sup>80</sup> No clinical trials of CoQ10 supplementation in hyperthyroid patients have been conducted.

### **Periodontal Disease**

Gingival biopsies yield subnormal tissue levels of CoQ10 in patients with periodontal disease.<sup>5</sup> Supplementation with CoQ10 has been shown to speed healing after periodontal surgery so significantly that, 5-7 days post-biopsy, the original biopsy site was difficult to locate.<sup>81-83</sup>

### **Renal Failure**

A randomized, double-blind, placebo-controlled trial was conducted on 48 patients with renal failure and 49 controls. Approximately half the subjects in each group required dialysis and all subjects were on standard therapy (40-120 mg furosemide daily). Patients received 180 mg CoQ10 or placebo daily for four weeks. CoQ10 therapy reduced serum creatinine and blood urea nitrogen (BUN) values and increased creatinine clearance and urinary output in approximately 80 percent of patients. The need for dialysis treatments was also reduced.<sup>84</sup>

### **Friederich's Ataxia**

An open-label, pilot trial explored the use of 400 mg CoQ10 plus 2,100 IU vitamin E daily in 10

patients with Friederich's ataxia for 47 months. A sustained improvement in mitochondrial energy synthesis was observed that was associated with a slowing of disease progression and improved cardiac function.<sup>85</sup>

### **Migraine**

Evidence indicates impaired energy metabolism may be present in brains of migraine sufferers. Rozen et al supplemented migraine patients with 150 mg CoQ10 daily for three months and demonstrated a 50-percent reduction in number of days with migraine headache, regardless of whether patients experienced aura or not.<sup>86</sup>

### **Pregnancy**

Plasma CoQ10 levels rise with each trimester of pregnancy and fetal wasting with subsequent spontaneous abortion has been correlated with low levels of CoQ10.<sup>87</sup>

### **Veterinary Indications**

Supplementation with CoQ10 may be of benefit to dogs and cats with cardiac disease.<sup>88</sup> Regeneration of damaged skeletal muscle has been observed in pigs supplemented with CoQ10 and vitamin E.<sup>89</sup> Coenzyme Q10 has also been shown to be one of the best antioxidants for equine laminitis, possibly due to its ability to inhibit the arachidonic acid pathway and subsequent formation of inflammatory prostaglandins.<sup>90</sup> Anecdotal reports indicate pain decreases rapidly when CoQ10 is administered without concurrent non-steroidal anti-inflammatory drugs. The therapeutic dose is 300-600 mg daily for two weeks, followed by a slow decrease to a maintenance dose of 100 mg daily.<sup>91</sup>

### **Dosage**

Typical dose of CoQ10 for most conditions is 60-200 mg daily in divided doses. Two studies on breast cancer used 390 mg daily and research examining the use of CoQ10 in Parkinson's disease and other neurological conditions found doses ranging from 400-2,400 mg daily to be effective.<sup>49</sup>





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### Drug-Nutrient Interactions

Cholesterol-lowering drugs such as lovastatin and pravastatin inhibit the enzyme HMG-CoA reductase, required for synthesis of cholesterol as well as CoQ10, resulting in decreased serum CoQ10.<sup>92</sup> Beta blockers propranolol and metoprolol<sup>93,94</sup> and phenothiazines and tricyclic antidepressants<sup>95</sup> have been shown to inhibit CoQ10-dependent enzymes.

### Toxicity

CoQ10 appears to be quite safe, even at the highest doses cited in the literature. Occasional reports of nausea, anorexia, or skin eruptions have been reported with CoQ10 supplementation.

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