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REVIEW

# Ubiquinol (Reduced Coenzyme Q10): A novel yet ubiquitous nutrient for heart disease

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**Coenzyme Q10 (CoQ10) is a ubiquitous nutrient in human cells where it is essential for mitrochondrial energy production. CoQ10 exists in both an oxidized (ubiquinone) and reduced form (ubiquinol), with ubiquinol being the bioactive form. In addition to its use in cellular ATP production ubiquinol acts as a powerful lipid-soluble antioxidant that protects lipid membranes and lipoproteins from oxidative stress. Lower circulating levels of ubiquinol are found in patients with cardiomyopathy and congestive heart failure (CHF) with deficiency being greater with increasing severity of disease. CoQ10 supplementation is well tolerated and without toxicity or drug interactions and there is evidence to suggest that CoQ10 supplementation may provide clinical improvements for patients with CHF patients as well as for patients with hypertension, statin-induced myopathy and for those undergoing cardiac surgery. Most research to date has focused on ubiquinone rather than ubiquinol, which has only recently become available as a supplemental nutrient. Effective doses of ubiquinol for congestive cardiac failure range from 100mg to 600mg/day yet most research to date has been limited to relatively small, short-term, and potentially biased trials that have used low doses of ubiquinone rather than ubiquinol. The evidence of clinical benefits with CoQ10 supplementation in cardiovascular disease is largely inconclusive and further large-scale trials are required to determine if the higher bioavailability and more potent activity of ubiquinol produces better clinical responses than ubiquinone. Ubiquinol therefore remains an interesting non-prescription, nutritional supplement that may be a useful adjunctive therapy for cardiac complaints despite not yet being recognized as a form of standard care.**

***Keywords:*** Coenzyme Q10; ubiquinone; ubiquinol; heart disease; hypertension

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## Introduction

### CoQ10: A Ubiquitous Energy Producer And Anti-oxidant

Coenzyme Q10 is fat-soluble vitamin-like nutrient that plays an essential role in the body's energy production processes through its role as an essential cofactor in the mitochondrial electron transport system and ATP production. CoQ10 is ubiquitous in all human cells (hence its name), with the highest concentrations found in the heart, liver and kidney where energy requirements are greatest. CoQ10 levels vary over the lifespan with levels in most tissues peaking at around age 20 and declining thereafter [1].

CoQ10 exists in an oxidized form (ubiquinone) that must be converted into the biologically-active, reduced form (ubiquinol) before being utilized [2]. Ubiquinol is a powerful and unique anti-oxidant that is the only known lipid soluble antioxidant animal cells can synthesize de novo and regenerate from its oxidized form. Ubiquinol can also serve to regenerate vitamin E from the tocopheroxyl radical, which must otherwise rely on water-soluble agents such as vitamin

C[3]. Ubiquinol therefore plays a vital role in cellular defenses against oxidative damage by stabilising mitrochondrial and other cell membranes and inhibiting the oxidation of LDL-cholesterol, which is of vital importance in the prevention of atherosclerosis [4].

**Sources**

CoQ10 is naturally synthesized by the body and can be obtained in an oxidised or mixed form from the diet in foods such as corn, nuts, soy, broccoli, meat and fish. Carnivorous diets are likely to be higher in CoQ10 and absorption varies greatly depending on the amount and types of foods eaten and increases with the amount of fat present. Oxidized CoQ10 is poorly absorbed due to its large molecular weight with more than 60% of an oral dose being excreted in faeces[5].

The main source of industrially-produced CoQ10 is yeast fermentation, which produces the same 'all-trans' isomers that occurs naturally in foods. Recently ubiquinol has become available as a supplement, which can be taken up by the body more quickly and has much greater bioavailability and biological activity than the previously available oxidised forms [6].

**Supplementation Dosage And Dose Forms**

Supplementation with either ubiquinol or ubiquinone increases ubiquinol levels in plasma lipoproteins and the heart and thereby enhances resistance of LDL to free radical oxidation[7] and cardiac ATP production[8]. The higher bioavailability and biological activity of ubiquinol however, increases its beneficial effects[2]. This was demonstrated in a cross-over trial that involved 4 weeks of supplementation with either 200mg/day of ubiquinol or ubiquinone. While both forms significantly increased total plasma CoQ10 ($P<0.001$), the increase with ubiquinol was nearly twice that produced by ubiquinone with serum levels increasing from 0.9 to 2.5μg/mL with ubiquinone and from 0.9 to 4.3μg/mL with ubiquinol. This study also found that plasma ubiquinol/total CoQ10 ratio increased significantly from baseline during ubiquinol supplementation ($P<0.005$), yet remained unchanged after ubiquinone supplementation [9].

Maximum serum concentrations of CoQ10 appear to stabilize after approximately three to four weeks of daily use. Most research to date has been on the use of ubiquinone for Congestive Heart Failure (CHF), yet an optimal dose for the treatment of CHF has not yet been established. While it is suggested that blood plasma levels of CoQ10 > 2.5 mg/l are required in order to effectively treat CHF as well as New York Heart Association (NYHA) class III and IV patients,[6] many past studies have used doses of 100mg of ubiquinone which are likely to be suboptimal for the majority of patients. It is therefore suggested that due to individual variation in absorption, direct supplementation with ubiquinol using flexible dosing schedules ranging from 100 to 600 mg per day are required to produce clinically effective plasma levels[6].

**CoQ10 And Heart Disease**

There are many reasons to suggest that ubiquinol may be beneficial in heart disease. The high energy requirements of cardiac muscle means that ubiquinol deficiency may be a risk factor for cardiovascular disease and relatively low myocardial tissue levels have been reported in cardiomyopathy and other cardiovascular diseases[10]. People suffering from CHF have also been found to have a lower ubiquinol content in their blood and heart muscle, with deficiency being greater with increasing severity of disease [11]. Observational studies further suggest that the plasma ubiquinol concentration is an independent predictor of mortality in patients with CHF[12] and this is supported by the finding that cardiac patients are more exposed to, or are more susceptible to, free radical reactions compared with healthy controls [13].

The first sign of lipoprotein exposure to oxidative stress is a reduced ubiquinol/ubiquinone ratio and compared to healthy controls, ubiquinol levels have been found to be lower in hyperlipidaemic patients with and without complications, such as coronary heart disease, hypertension, or liver disease[14]. Ubiquinol supplementation may therefore provide vital anti-oxidant support in addition to correcting any deficiency. More recent data suggests that ubiquinol may also help to counteract endothelial dysfunction through both anti-oxidant and anti-inflammatory actions[15,16]. This suggests that supplementation with ubiquinol may further support cardiac function by improving coronary blood supply [17].

While most research on CoQ10 has focused on its role in reducing oxidative stress and enhancing cardiac energy production, studies also suggest an effect in improving subjective fatigue and physical performance and opposing exercise-related damage in trained and untrained athletes [2,18,19].

**Clinical Studies In Heart Disease**

Positive clinical and haemodynamic effects of oral CoQ10 supplementation have been observed in double-blind trials, especially in CHF[10]. At least 39 open trials with CoQ10 supplementation in heart failure have been published,

involving 4498 patients, albeit with varying results. Most studies to date have been done with ubiquinone rather than ubiquinol and negative or inconclusive results have been attributed to small sample sizes, low dosages, short-term study periods and supplementation in late stages of CHF [6].

A recent meta-analysis of 13 randomised controlled trials suggests that CoQ10 may significantly improve the Ejection Fraction in patients with CHF and improve NYHA class[20]. This meta-analysis however is only based on short term, single center studies (mostly 12 weeks) using ubiquinone and replication of these results in large scale, long term trials is required before conclusive clinical recommendations can be made. More recently a Cochrane review analyzed seven studies with 914 participants comparing the use of CoQ10 versus placebo for heart failure, however the large heterogeneity, small sample sizes and lack of clinical endpoints prevented the authors from making any definitive conclusions [21].

## CoQ10 For Hypertension

The ability of ubiquinol supplementation to deliver higher levels of bioactive CoQ10 to the heart and circulating lipoproteins, provides a rationale for using ubiquinol as an adjunct or alternative to conventional agents in the treatment of hypertension [6,22,23]. This is supported by evidence from a meta-analysis of 12 clinical trials that included three randomized controlled trials, one crossover study and eight open label studies involving 362 patients that concluded CoQ10 has the potential to lower systolic blood pressure by up to 17 mm Hg and diastolic blood pressure by up to 10 mmHg in hypertensive patients[24].

A more recent Cochrane review of three randomized, placebo-controlled clinical trials with a total of 96 participants found a clinically significant blood pressure lowering effect of coenzyme Q10 that appears to be larger than other available blood pressure lowering drugs. The limited nature of the data and possibility of bias however prevented the authors from making any firm conclusions other than to suggest that current results are sufficiently consistent and encouraging to warrant larger trials[25].

## CoQ10 And Cardiac Surgery

In addition to assisting in CHF and hypertension, supplementation with ubiquinol maybe an effective pre-operative therapy when given for 1-2 weeks prior to cardiac surgery. Preoperative oral coenzyme CoQ10 therapy has been shown to increase myocardial and cardiac mitochondrial coenzyme CoQ10 levels, improve mitochondrial efficiency, and increase myocardial tolerance to in vitro hypoxia-reoxygenation stress[8]. There is also evidence to suggest CoQ10 can reduce reperfusion injury, reduce surgical complications and accelerate recovery times [26].

Preoperative supplementation with ubiquinol may therefore be an important consideration for any patient undergoing elective cardiac surgery and this may be more important for older patients who have lower circulating ubiquinol levels and who generally do not respond as well to surgery as younger patients, possibly due to age-related reductions in cellular energy production [26].

## CoQ10 And Statin-Induced Myopathy

Stain drugs act by inhibiting the production of mevalonate, a precursor of both cholesterol and CoQ10 and studies have shown statin therapy leads to reduced levels of circulating CoQ10 [27] with reductions up to 40% [28]. This has led to speculation that reduction in CoQ10 concentrations may be an important factor in statin-related myopathies[29] and this is supported by the finding that supplementation with CoQ10 reverses statin-induced decreases in circulating CoQ10 concentrations and reduces symptoms of statin-induced myopathy[5,30]. Direct supplementation with ubiquinol may therefore provide a safe and effective strategy for treating statin-induced fatigue or myopathy, yet current evidence is deemed insufficient to support routine supplementation to prevent the adverse effects of statin therapy [29].

## Conclusion

Current evidence suggests that CoQ10 is without toxicity or drug interactions yet evidence is still inconclusive regarding its use as an adjunctive therapy for cardiovascular disease. The higher activity and bioavailability of ubiquinol suggests that it has advantages over ubiquinone, yet few rigorous studies have been done and large, long-term studies are needed on ubiquinol before clinical recommendations can be made. Ubiquinol therefore remains an interesting but experimental non-prescription nutritional supplement that may be a useful adjunctive therapy for cardiac complaints despite not being recognized as standard care.

## The Conflict Of Interest Statement

The author received an honorarium to cover time spent preparing this article. This entire article however, is the independent work of the author and the sponsors did not have any input into the article's content. There are no other potential conflicts.

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