

Coenzyme Q10 supplementation for diabetes and its complications: an overview

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Abstract

This article reviews the potential role of dietary supplementation with coenzyme Q10 (CoQ10) for the management of patients with type 2 diabetes. The rationale for supplementation with CoQ10 is based on its key roles in cellular energy metabolism and as an antioxidant, and its potential mediation of oxidative stress and inflammation, which have been implicated in the pathogenesis of diabetes. Randomised controlled clinical trials have demonstrated that supplementation with CoQ10 can significantly improve glycaemic control, as well as improving vascular dysfunction. Supplementation with CoQ10 may be of particular importance in type 2 diabetics prescribed statins and in those with fatty liver disease. Supplemental CoQ10 is usually well tolerated, with no significant adverse effects reported in long-term use. The importance of product quality and bioavailability cannot be over-emphasised, since this may be a factor in the disparity of findings from clinical trials supplementing CoQ10.

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Key words: coenzyme Q10, diabetes, glycaemic control, vascular dysfunction, statins, fatty liver disease

Introduction

This article focuses principally on the potential role of dietary supplementation with coenzyme Q10 (CoQ10) in type 2 diabetes in human subjects, both with respect to the primary defect of compromised glycaemic control and the secondary consequences relating to vascular dysfunction and organ damage. The link between CoQ10, diabetes and fatty liver disease is also discussed. Although work has been carried out to investigate the action of supplementary CoQ10 in animal models of diabetes¹⁻³ and in uncontrolled human studies,⁴ this article is concerned with recent randomised controlled clinical trials unless otherwise indicated.

Coenzyme Q10 (CoQ10)

CoQ10 is a vitamin-like substance which plays a key role in the

biochemical process that supplies all cells with the energy required for their normal functioning; this is of particular importance in tissues with a high energy requirement, such as the heart. CoQ10 is also important as a lipid soluble antioxidant, protecting cells from the potentially damaging effects of toxic free radical species generated during normal cellular metabolism (oxidative stress).

CoQ10 occurs within the body in two very closely related chemical forms, an oxidised form (ubiquinone) and a reduced form (ubiquinol). The chemical structure of CoQ10 is relatively complex, and ubiquinol differs from ubiquinone only by the addition of an extra two hydrogen atoms. Some supplement manufacturers claim that ubiquinol is the more important bioactive form of CoQ10; this is incorrect because, although CoQ10 is transported in blood in the reduced ubiquinol form, it is continually interconverted between oxidised and reduced forms within cells, and thus ubiquinone and ubiquinol CoQ10 forms are of equal metabolic importance.

Most of the body's daily CoQ10 requirement is synthesised endogenously, with a relatively small proportion obtained from the normal diet. Based on a total body pool of 2 g and average tissue turnover time of 4 days, the requirement for CoQ10 has been estimated at 500 mg/day. A relatively small proportion of this daily requirement is obtained from the normal diet, typically up to 5 mg/day.⁵ As people age, the capacity of the body to produce CoQ10 declines continuously; optimal production occurs around the mid-twenties, with a continual decline thereafter (by approximately 50% at age 60).

An adequate supply of CoQ10 is essential for normal functioning of mitochondria (the subcellular organelles present in all cells where energy generation takes place), and CoQ10 depletion, oxidative stress and mitochondrial dysfunction have been implicated in the pathogenesis of diabetes.^{6,7}

Effect of CoQ10 on blood glucose control

Several studies have reported significantly reduced blood CoQ10 levels in type 2 diabetic patients, correlating with increased levels of plasma glucose, HbA_{1c} and markers of oxidative stress.⁸ It has been proposed that, in older patients with type 2 diabetes (in whom blood CoQ10 levels have become depleted to 0.35 µg/ml or less) and who have become refractory to hypoglycaemic drugs, supplementation with CoQ10 is most effective; in particular, the subsequent response to hypoglycaemic drugs is significantly improved (W Judy, unpublished data).

Earlier randomised controlled clinical studies to determine the effect of CoQ10 supplementation on glycaemic control in type 2 diabetics gave mixed results. Thus Eriksson *et al*⁹ reported that supplementation with CoQ10 (200 mg/day for 6 months) did not affect

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glycaemic control whilst Hodgson *et al*¹⁰ found CoQ10 supplementation (200 mg/day for 3 months) significantly improved long-term glycaemic control (mean HbA_{1c} reduced by 0.4% vs. placebo) and blood pressure (reductions in mean systolic blood pressure of 6 mmHg and diastolic blood pressure of 3 mmHg, respectively, vs. placebo).

In more recent randomised controlled studies, Kolahdouz-Mohammadi *et al*¹¹ reported CoQ10 supplementation (200 mg/day for 3 months) significantly reduced HbA_{1c} levels (mean HbA_{1c} reduced by 0.6% vs. placebo) in type 2 diabetics. Similarly, Zahedi *et al*¹² found that CoQ10 supplementation (150 mg/day for 3 months) significantly improved fasting plasma glucose (mean FPG reduced by 2.05 mmol/L (37 mg/dL) vs. placebo) and HbA_{1c} levels (mean HbA_{1c} reduced by 0.8% vs. placebo), and Hosseinzadeh-Attar *et al*¹³ reported significant improvement in HbA_{1c} levels (mean HbA_{1c} reduced by 0.5% vs. placebo) following supplementation with 200 mg/day for 3 months. In type 2 diabetic patients with neuropathy, supplementation with CoQ10 (200 mg/day for 3 months) did not significantly benefit neuropathic symptoms, HbA_{1c} or fasting glucose levels, but reduced inflammation and increased insulin sensitivity.¹⁴ Serum insulin and glucose homeostasis parameters were significantly improved in patients with metabolic syndrome/type 2 diabetes following CoQ10 supplementation (100 mg/day for 2 months).¹⁵ In overweight or obese patients with type 2 diabetes, supplementation with CoQ10 (200 mg/day for 3 months) significantly reduced HbA_{1c} levels (mean baseline HbA_{1c} reduced by 0.7%) and decreased weight and waist circumference.¹⁶

The question arises as to how CoQ10 might directly influence glycaemic homeostasis. In general terms, the metabolism of glucose involves a number of energy-dependent processes; if the body's energy supply mechanism is compromised via mitochondrial dysfunction/coenzyme Q10 deficiency, then it follows that glycaemic control must be affected. More specifically, CoQ10 has been shown to mediate directly the expression of over 100 genes involved in cellular metabolism, and data from diabetic animal models have shown CoQ10 can modulate components of the insulin signalling pathway (insulin receptors, tyrosine kinase and phosphatidylinositol kinase), glucose metabolism (glucose transporters, adiponectin) and oxidative stress (malondialdehyde).¹⁷

Effect of CoQ10 supplementation on vascular dysfunction

Type 2 diabetes is characterised by increased risk of damage to blood vessels throughout the body, resulting in the long term in ulceration of the feet and lower legs, renal failure, heart failure and nerve damage. For example, diabetic retinopathy typically develops in some 60% of type 2 diabetics over a period of approximately 20 years. Increased blood glucose levels cause glycation of vessel wall proteins resulting in endothelial cell dysfunction, as well as changes in erythrocyte aggregation/adhesion characteristics. Damage to blood vessels is linked to free radical-induced damage resulting from diabetic-related oxidative stress and its associated inflammation.

Increased oxidative stress in type 2 diabetes correlates with reduced CoQ10 levels.¹⁸ Markers of oxidative stress, including

oxidised LDL cholesterol and the redox regulating protein glutaredoxin, were significantly improved in patients with type 1 and type 2 diabetes following CoQ10 supplementation (200 mg/day for 3 months).¹⁹ Supplementation with CoQ10 (200 mg/day for 3 months) in type 2 diabetics significantly improved endothelial dysfunction, quantified via brachial artery flow-mediated dilation, translating as a 10–20% reduction in residual cardiovascular risk.²⁰ Hosseinzadeh-Attar *et al*¹³ found CoQ10 supplementation (200 mg/day for 3 months) significantly reduced circulatory levels of asymmetric dimethylarginine, a marker of endothelial dysfunction and cardiovascular event risk factor. In the Q-SYMBIO study (a randomised double-blind multicentre trial of CoQ10 as adjunctive treatment of chronic heart failure with focus on SYMptoms, BIO-marker status and long-term outcome), supplementation with CoQ10 (300 mg/day for 2 years) improved heart function and reduced cardiovascular-related mortality by 43% in heart failure patients, 10% of whom had type 2 diabetes.²¹ Similarly, in the KISEL-10 study (a 5-year prospective randomised double-blind placebo-controlled trial of the effect of intervention with selenium and CoQ10 on cardiovascular mortality and cardiac function in the elderly population in Sweden), supplementation with 200 mg/day CoQ10 and 200 µg/day selenium for 5 years reduced cardiovascular mortality by 53% in elderly subjects, 20% of whom had diabetes.²²

CoQ10, statins and diabetes

It is generally recognised that there is an increased risk (depending on a number of factors) of approximately 10% of developing type 2 diabetes in patients prescribed statins (particularly simvastatin).²³ However, Cederberg *et al*²⁴ have recently quoted an increased risk of 46% of developing type 2 diabetes in patients prescribed statins (simvastatin, atorvastatin), resulting from decreased insulin secretion/sensitivity. It is of note that simvastatin and atorvastatin are the two statin types which induce the greatest reductions in CoQ10 synthesis within the body; as well as reducing endogenous synthesis of cholesterol, statins also inhibit the production of CoQ10 which is synthesised via the same biochemical pathway. Statin-induced diabetes has been linked to reductions in circulatory adiponectin and CoQ10 levels, and a reduction in the protein glucose transporter type 4 (GLUT4), which helps insulin to control blood glucose levels.²⁵ In cell culture, administration of CoQ10 prevents the reduction in GLUT4 protein levels caused by simvastatin,²⁶ although these findings need to be confirmed in human subjects.

CoQ10, diabetes and liver disease

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder worldwide, with a prevalence in the general population estimated at 20–30%. Estimation of the incidence of NAFLD in diabetes varies with the population studied and analytical method used (biochemical, histological, ultrasonography or magnetic resonance imaging). In those with type 2 diabetes, this has been estimated by some authorities to be as high as 70%, rising to 90% in those with morbid obesity.^{27,28}

Although CoQ10 is synthesised throughout the body, because of its size and high metabolic capacity, the liver is the major site of CoQ10 synthesis. In patients with liver disease

where metabolic capacity has been compromised, reduction in CoQ10 production is likely to have a deleterious effect on heart function. Thus, NAFLD is a risk factor for cardiovascular disease, which has been reported to be one of the major causes of death in NAFLD patients.²⁹ NAFLD is associated with heart failure, arrhythmias, valve dysfunction and atherosclerosis.³⁰ Reduced CoQ10 levels may be a particular problem in patients with fatty liver disease prescribed statins since, in addition to inhibiting cholesterol synthesis, statins also inhibit the production of CoQ10.

In addition to its role in cellular energy production and as an antioxidant, CoQ10 has been shown to directly influence the expression of a number of genes, including those involved in inflammation and oxidative stress.^{31,32} Thus, as well as reducing the risk of cardiovascular problems in patients with liver disease, CoQ10 supplementation may also benefit the disease process within the liver by reducing inflammation and oxidative stress, key factors in the pathogenesis of NAFLD.³³

Yesilova *et al*³⁴ found that blood CoQ10 levels were depleted in NAFLD patients, with the decrease in CoQ10 correlating with increased liver inflammation and cirrhosis. A randomised controlled trial by Farhangi *et al*³⁵ found supplementation with CoQ10 (100 mg/day for 4 weeks) resulted in decreased systemic levels of biochemical markers of inflammation and oxidative stress. In a more recent randomised controlled trial,³⁶ NAFLD patients given 100 mg CoQ10 per day for 3 months showed significant reductions in the levels of blood markers for liver inflammation and damage (aspartate aminotransferase, gamma-glutamyl peptidase, C-reactive protein).

It follows from the above that diabetes, NAFLD and cardiovascular disease are interlinked, with deficiency of CoQ10 as a common denominator.

Safety of CoQ10

CoQ10 is generally well tolerated, with no serious adverse effects reported in long-term use. Very rarely, individuals may experience mild gastrointestinal disturbance. There are no known toxic effects, and CoQ10 cannot be overdosed.^{37,38} The safety of CoQ10 has been confirmed in more than 200 randomised controlled trials in a wide range of disorders. Several case studies have suggested that CoQ10 may interfere with the action of warfarin; however, a randomised controlled clinical trial showed CoQ10 supplementation at 100 mg/day had no effect on the clinical action of warfarin.³⁹

Because food supplements are not regulated in the same way as prescription medicines, concerns have been raised regarding the potential variability of various CoQ10 supplements used in clinical trials; in particular, there is a common misconception amongst healthcare professionals that there are no regulatory agency approvals for CoQ10.⁴⁰ This is incorrect, as one CoQ10 product has a Marketing Authorisation within the EU for the adjuvant treatment of chronic heart failure. As part of the licensing procedure, periodic safety update reports (PSURs) have to be submitted every 3 years. In a sample PSUR, over a 3-year period the supply of 1.4 million daily doses, equivalent to 3,900 person-years usage, did not result in any reported serious adverse events ascribable to CoQ10.



Key messages

- There is a potential role for dietary supplementation with coenzyme Q10 in the management of patients with type 2 diabetes
- Controlled clinical trials have shown significant benefits in glycaemic control and vascular function following CoQ10 supplementation
- CoQ10 supplementation may be of particular benefit in patients prescribed statins or those with fatty liver disease

CoQ10: importance of product quality and bioavailability

Bioavailability is defined as the proportion of an ingested substance that reaches the blood circulation. Because of its relatively large molecular size and lipid solubility, the bioavailability of CoQ10 is intrinsically low. CoQ10 is absorbed from the intestinal tract by the same mechanism as other lipid soluble nutrients, via a lipid carrier through mucosal cells initially into the lymph, and thence into the bloodstream; thus absorption is optimised when CoQ10 is dissolved in a carrier oil (preferably soya or palm oil). The delayed peak concentration of CoQ10 in blood is a consequence of this initial absorption into the lymphatic system. However, incorporation of supplemental CoQ10 in liposomal, micellar or nanoparticle form cannot increase the absorption of CoQ10 through intestinal cells into the lymph. CoQ10 cannot be made more water soluble, as any alteration to the molecular structure means that the molecule is no longer CoQ10. When supplemental CoQ10 is first produced (via a yeast fermentation process), it is obtained in the form of crystals which cannot be absorbed from the digestive tract. It is essential that these crystals are dispersed into single CoQ10 molecules (and remain dispersed during the product shelf-life) to enable optimum bioavailability; adding CoQ10 crystals to a carrier oil without such dispersal, a cost-saving technique used by some manufacturers, is inadequate. Disparity in the findings of clinical trials supplementing CoQ10 in diabetes may result from a number of factors, including inadequate bioavailability and insufficient dosage or treatment duration, as well as inter-individual variation in the ability to absorb CoQ10.

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