Review

Effects of coenzyme Q10 on vascular endothelial function in humans: A meta-analysis of randomized controlled trials

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Abstract

Objective: The purpose of this study was to quantify the effect of coenzyme Q10 on arterial endothelial function in patients with and without established cardiovascular disease.

Background: Endothelial dysfunction has been implicated in the pathogenesis of atherosclerosis.

Methods and results: The search included MEDLINE, Cochrane Library, Scopus, and EMBASE to identify studies up to 1 July 2011. Eligible studies were randomized controlled trials on the effects of coenzyme Q10 compared with placebo on endothelial function. Two reviewers extracted data on study characteristics, methods, and outcomes. Five eligible trials enrolled a total of 194 patients. Meta-analysis using random-effects model showed treatment with coenzyme Q10 significantly improved in endothelial function assessed peripherally by flow-mediated dilatation (SMD 1.70, 95% CI: 1.00–2.4, p < 0.0001). However, the endothelial function assessed peripherally by nitrate-mediated arterial dilation was not significantly improved by using fix-effects model (SMD –0.19, 95% CI: −1.75 to 1.38, p = 0.81).

Conclusion: Coenzyme Q10 supplementation is associated with significant improvement in endothelial function. The current study supports a role for CoQ10 supplementation in patients with endothelial dysfunction.

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1. Introduction

Atherosclerosis and ischaemic heart disease are the major source of morbidity and mortality in the developed world, representing the result of several underlying mechanisms and closely related to endothelial function [1,2]. Endothelial dysfunction, characterized by a decrease in vascular reactivity, is considered to be an early marker for atherosclerosis and is highly prognostic of future cardiovascular events [3–7]. Preliminary studies have also demonstrated that restoration of normal endothelial function is associated with reduction of cardiovascular events [8,9]. Thus, assessment of endothelial function is emerging as a key adjuvant tool to stratify patients at risk for cardiovascular events. The flow-dependent endothelial-mediated dilation (FMD), a functional parameter commonly used as a biomarker of vascular function, is currently, medical therapy to improve endothelial function is needed.

Coenzyme Q10 (CoQ10) is a potent physiological antioxidant which is part of the mammal mitochondrial electron transport chain, and was found to be a potent lipophilic antioxidant [10]. CoQ10 is obtained both through tissue synthesis and diet [11]. Supplementary oral administration of CoQ10 has been demonstrated to increase CoQ10 levels in plasma, white blood cells and platelets [12]. The effect of CoQ10 supplementation has been widely studied in patients with cardiovascular risk factors. CoQ10 has been shown to positively affect heart performance in congestive heart failure [13–15] and ischemic heart disease [16], and has been shown a clinically significant blood pressure lowering effect [17–19]. Recently, the effect of oral CoQ10 supplementation on endothelial function in patients with coronary artery disease [20], heart failure [21], and diabetes mellitus [22] has been investigated by many studies. However, the results of these studies were not consistent, and the sample sizes were relatively small. As a result, the precise effect of CoQ10 supplementation has not been established.

To quantify the endothelial function improving effect of CoQ10, we performed a meta-analysis of currently available data from human randomized controlled trials that focused on the effect of CoQ10 consumption on endothelial function as measured by FMD of the brachial artery. The information derived from this analysis should assist clinicians in determining whether it is worth trying CoQ10 as a therapeutic intervention to improve endothelial function.

2. Methods

2.1. Strategy to search randomized trials

The Database of Abstracts of Reviews of Effectiveness (DARE) and the Cochrane Database of Systematic Reviews were searched for relevant reviews. We searched MEDLINE (1966–July 2011), the Cochrane Library and EMBASE (1982–July 2011) for randomized clinical trials that compared CoQ10 with a control group and measured the mean change in endothelial function level and the variance of the change. In addition we examined the reference lists and related links of retrieved articles in PubMed to detect studies potentially eligible for inclusion. No language restrictions were used.

The following search terms were used to search in titles and abstracts: (Coenzyme Q10 or CoQ10 or coenzyme Q) and (flow-mediated or flow mediated or FMD or endothelial function or endothelial dysfunction or endothelium-dependent or blood flow or arterial stiffness or vascular resistance). The search was limited to studies in human adults.

2.2. Study selection

2.2.1. Inclusion criteria

(1) Study design had to meet the following criteria: randomized, placebo-controlled parallel or crossover trial; duration of treatment of at least four weeks; (2) population enrolled were adults 18 years or above; (3) the intervention group received a CoQ10; the comparison group received placebo; and (4) the data regarding the measurement of the mean initial and final peripheral endothelial function.

2.2.2. Exclusion criteria

Studies were excluded if outcome measures of endothelial function did not include both the mean change in endothelial function and the variance of the change or if we were unable to obtain adequate details of study methodology or results from the article or study investigators.

2.3. Data collection and analysis

2.3.1. Selection of studies

Two investigators (Gao LG and Mao QX) independently assessed and abstracted pertinent data from trials in duplicate using a standardized pre-defined form. The initial screen for potential relevance excluded articles whose titles and/or abstracts were clearly irrelevant. We extracted data on population characteristics (age, sex, and baseline comorbidities), intervention (dose of CoQ10, duration of treatment), the mean initial and final brachial artery FMD and nitroglycerin-mediated dilatation (NMD), and the methodological quality of the trials. A third reviewer resolved discrepancies. The change and variability in endothelial function after CoQ10 treatment compared with placebo were calculated using previously described methods [23].

Our primary outcome was the percentage change in FMD between baseline and final levels due to CoQ10 supplementation. The Secondary outcome was the percentage change in endothelium-independent brachial artery NMD due to CoQ10 treatment compared to that due to placebo. Mean change is FMD or NMD value at the end of the intervention minus the FMD or NMD value at the start of the intervention. If the percentage change in brachial artery FMD and NMD was not reported in the study, we calculated it according to the Cochrane Handbook for Systemic Review and Follman D’s theory for overview of clinical trials with continuous variables [24]. We assumed a within-subject correlation coefficient of 0.5 [25].

Study quality was independently assessed (by Gao LG and Mao QX) according to a tool that was specifically developed for this meta-analysis based on the Delphi Consensus [26]. The following criteria were used for scoring the quality of each study: The nine criteria were: (a) Was a method of randomization performed? (b) Was the treatment allocation concealed? (c) Were the groups similar at baseline regarding the most important prognostic indicators? (d) Were the eligibility criteria specified? (e) Was the outcome assessor blinded? (f) Was the care provider blinded? (g) Was the patient blinded? (h) Were point estimates and measures of variability presented for the primary outcome measures? (i) Did the analysis include an intention-to-treat analysis? A combined quality score was obtained by adding the scores for each criterion. Thus, quality score could range from 0 to 9 points.

It was not possible to do the subgroup analyses due to the small number of included trials. Publication bias was assessed visually by examining for funnel plot asymmetry.
2.4. Statistical analysis

Our meta-analysis and statistical analyses were performed with Stata software (version 10.0; Stata Corporation, College Station, TX) and REVMan software (version 5.0; Cochrane Collaboration, Oxford, United Kingdom). The heterogeneity of the five studies was examined by Cochran chi-square tests. The Mantel–Haenszel [27] fixed-effect model or the random-effects (DerSimonian and Laird) model [28] was chosen for meta-analysis of the comparison of the percentage change in brachial artery NMD or FMD due to CoQ10 treatment compared to that due to placebo. We calculated the standardized mean difference (SMD) with 95% confidence intervals for net change in the endothelial function measure using the values of the outcomes (brachial artery FMD and NMD) from beginning to end of the treatment with a variance estimator. Publication bias was evaluated using both the Begg’s funnel plot and the Egger plot. To identify the possible source of heterogeneity within these studies, we excluded studies one by one. p values that were <0.05 were considered statistically significant. All statistical tests were two-sided.

3. Results

3.1. Search results and trial flow

The combined search of MEDLINE, EMBASE, BIOSIS1, Scopus and Cochrane Library identified 59 articles. Based on the predefined selection criteria, 54 papers were excluded for different reasons (Fig. 1). A total of 5 studies were retrieved for this meta-analysis (Table 1). Two studies had a crossover design [22,29] and three a parallel design [20,30,31].

3.2. Study characteristics

Table 1 shows the characteristics of the 5 included studies. In total, 194 participants were randomized, of whom 97 were allocated to CoQ10 therapy and 97 to control. The number of participants in the trials ranged from 24 to 56. Mean age ranged from 34.0 to 68.9 years and the duration ranged from 4 weeks to 12 weeks. Thirty-one percent of the participants were women, 44.3% had diabetes, 34.5% had hypertension, and 27.8% had established coronary artery disease. The mean baseline BMI ranged from 23 to 30 kg/m². The majority of the included studies were of high quality, with more than 80% scoring nine points on the Delphi consensus criteria. One of the included study determined FMD manually [29]. This method has been shown to be accurate and reproducible for measurement of small changes in arterial diameter, with low inter-observer error for measurement of FMD. The majority of the included studies determined FMD with the software with low intra-observer variability and inter-observer variability [20,22,30,31].

3.3. Effect of CoQ10 on FMD

In each of the individual studies, except for one [29], CoQ10 showed a statistically significant effect on FMD. CoQ10 therapy when compared to placebo improved %FMD by 1.70% (95% CI: 1.00–2.40; p < 0.00001; Fig. 2). No significant heterogeneity for this outcome was found ($I^2 = 52%$, $p = 0.08$).

3.4. Effect of CoQ10 on NMD

Compared with control group, CoQ10 therapy did not significantly improve % NMD (SMD = −0.19 with 95% CI: −1.75 to 1.38, $p = 0.81$) (Fig. 3). No significant heterogeneity for this outcome was found ($I^2 = 0%$, $p = 0.92$).
3.5. Publication bias

Funnel plots and Egger tests suggested no significant asymmetry in the meta-analyses of FMD and NMD. Begg’s funnel plot of SMD of FMD (Begg–Mazumdar test p = 0.806 and Egger test p = 0.353) and funnel plot of SMD of NMD (Begg–Mazumdar test p = 1 and Egger test p = 0.525) indicated that there are no strong evidences of publication selection bias.

4. Discussion

In this systematic review and meta-analysis, we summarized published evidence from 5 randomized, double-blind, placebo-controlled clinical trials that investigated the effect of CoQ10 therapy on endothelial function as measured by FMD and NMD. It was found that CoQ10 therapy substantially enhances FMD. The absolute increase in FMD of 1.70% after CoQ10 supplementation is of clinically significance, as an absolute improvement in FMD of 1% may already translate into a 10–25% reduction in residual cardiovascular risk for these patients [32,33]. However, CoQ10 treatment did not significant improve NMD. CoQ10 supplementation did not improve nitrate-mediated dilatation of the brachial artery, again suggesting no effect on endothelium-independent vasorelaxation.

Endothelial dysfunction plays a key role in the development, progression, and clinical manifestations of atherosclerosis and cardiovascular diseases. It can also be regarded as a syndrome whose systemic manifestations are associated with significant morbidity and mortality and can be improved with risk-reduction therapy. Consequently, endothelial function has been defined as an “excellent barometer” of vascular health and can be used to gauge cardiovascular risk [34]. FMD measurement by high-resolution ultrasonography is a broadly applicable method that is used for the examination of endothelial function [34]. FMD is designated as an endothelium-dependent process that reflects the relaxation...
CoQ10 is a key component of mitochondrial oxidative phosphorylation and adenosine triphosphate production. It has also been shown that CoQ10 located in the mitochondria, lysosomes, Golgi and plasma membranes has antioxidant activity either by directly reacting with free radicals or by regenerating tocopherol and ascorbate from their oxidized state [35]. In human pancreas and adrenal the CoQ10 content was highest at one year of age, whereas in other organs the corresponding peak value was at 20 years of age, and was followed by a continuous decrease upon further aging [36]. CoQ10 deficiency in various clinical conditions including heart disease, diabetes, myopathy, Huntington’s disease, Parkinson’s disease, reasonably constitutes one of the sound reasons for the therapeutic use of CoQ10 in human. Its clinical benefits are mainly due to its ability to improve ATP production, antioxidant activity and membrane stabilizing properties. Human studies examining the effect of CoQ10 on endothelial function of the peripheral circulation have yielded inconsistent results. Raitakari et al. studied 12 healthy hypercholesterolaemic subjects with endothelial dysfunction who received oral CoQ10 150 mg daily or placebo for 4 weeks in a double-blind crossover study, and showed that CoQ10 did not significantly increased FMD of the brachial artery (4.3% vs. 5.1%, p = 0.99), measured by ultrasound. However, CoQ10 supplementation improve FMD of the brachial artery in the studies conducted in the subjects with diabetes and/or coronary artery disease (CAD). The absolute increase in FMD of 1.70% after CoQ10 supplementation in the present meta-analysis demonstrates that CoQ10 therapy is associated with statistically significant improvement in peripheral endothelial function.

Evidence indicates that the optimal doses in heart disease appear to be 50–300 mg/day. CoQ10 was safe and well tolerated at doses up to 1200 mg/day [37]. The long-term safety and tolerability of CoQ10 administration in pharmacological dosages of 30–300 mg/day has been confirmed, with the only potential drug interaction recorded to date being antagonism of the action of warfarin due to the vitamin-K-like properties of CoQ10.

The beneficial effect of CoQ10 therapy in improving endothelial dysfunction is mainly due to its antioxidant activity, anti-inflammatory activity, and its ability to improvement of endothelial NO bioavailability [38,39]. Despite the fact that FMD is associated with enhanced NO production, the clinical data demonstrating changes in NO levels are rare. Recently, Tsai et al. [35] studied the effects of CoQ10 on protein expression of endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) as well as NO content and formation of nitrotyrosine. Their data suggested that pretreatment of CoQ10 suppressed the oxidized low-density lipoproteins (oxLDL) induced down-regulation of eNOS and up-regulation of iNOS, reduced the levels of nitrotyrosine. And it was demonstrated that CoQ10 suppressed the generation of ROS, which subsequently increased the bioavailability of nitric oxide (NO).

CoQ10 is a potent antioxidant [40,41]. Nevertheless, there are conflicting data on the effect of CoQ10 supplementation on oxidative stress. Tiano et al. [20] showed an improvement in endothelium-bound extra cellular super oxide dismutase (ecSOD) activity in subjects with coronary artery disease and the increase in ecSOD activity significantly correlated with the improvement in FMD. On the other hand, other studies failed to show any significant alteration in marker s of oxidative stress such as urinary 24-hurinary 20-hydroxyecosatetraenoic acid levels [22], plasma F2-isoprostane [22,30], and plasma soluble intercellular adhesion molecule [42] after CoQ10 supplementation. Dai et al. CoQ10 supplementation did not alter hs-CRP, serum superoxide dismutase or 8-isoprostanep; suggesting that the beneficial effects of CoQ10 on endothelial function are independent of changes in oxidative stress and systemic inflammation [31].

It is becoming increasingly apparent that inflammatory mediators play a crucial role in the development of endothelial dysfunction. OxLDL are pivotal molecules in the development of atherosclerosis in systemic autoimmune diseases and they should be considered a crucial pro-inflammatory stimulus which sustains chronic inflammation [43]. Once retained in the intima of the arteries, oxLDL activate endothelial cells and up-regulate the expression of adhesion molecules and the secretion of chemokines which contribute to the recruitment of circulating leukocytes [44]. When monocytes/macrophages infiltrate atherosclerotic plaques, they uptake oxLDL and form the “foam cells” that play a key role in the secretion of inflammatory mediators [45]. An important function of CoQ10 is protecting LDL from oxidation. Moreover, it reduces the levels of lipid peroxides associated with lipoproteins in atherosclerotic lesions. Furthermore, CoQ10 decreases the levels of B2-integrin CD11b in monocytes, which counteracts monocyte–endothelial cell interactions [46]. CoQ10 may suppress the production of proinflammatory substances, like nuclear factor κ B (NFκB)-gene expression and the production of pro-inflammatory cytokines [47,48].

Recently, peroxisomal proliferator activated receptor gamma coactivator (PGC-1alpha), a transcriptional regulator involved in mitochondrial biogenesis and respiration, has emerged as a new therapeutic target for cardiovascular disorders [49]. Mitochondrial CoQ10 (mitoQ) plays an important role in modulating reactive oxygen species-induced mitochondrial permeability transition and cell death. The antioxidant property of PGC-1alpha might hence be beneficial to maintain vasculature function and thus contribute to the prevention of cardiovascular diseases.

There are several limitations to this systematic review and meta-analyses. First, some potentially relevant studies were excluded from the analysis because of incomplete reporting on the outcome measure of endothelial function. Second, the study properties on population characteristics, dose, duration of treatment are different which directly effects the FMD. Heterogeneity of the studies in the meta analysis makes the comparison tender to bias. Third, our search of the literature led to the inclusion of only 5 studies and a relatively small number of subjects. Thus, large, long-term randomized trials may be needed to confirm the CoQ10-mediated improvement in endothelial function.

In conclusion, this study provides evidence that CoQ10 therapy improves endothelial function in patients both with and without overt cardiovascular disease. However, to what extent CoQ10-mediated improvement in endothelial function is indeed causally related to a reduction in cardiovascular events can only be determined by large, long-term randomized trials on clinical endpoints.

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**References**


