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Review article

Coenzyme Q10 – A new player in the treatment of heart failure?

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ABSTRACT

Coenzyme Q10 is the only endogenously synthesized lipid with a redox function which exhibits broad tissue and intracellular distribution in mammals. Beneficial effects of CoenzymeQ10 supplementation were observed in several age-related diseases including heart failure. CoQ10 (coenzyme Q10) level is significantly decreased in patients with this disease, which correlates with severity of clinical symptoms. Supplementation with various pharmaceutical formulations of CoQ10 improves impaired cardiac function and clinical course of heart failure. Current data from clinical trials indicate that CoQ10 can significantly reduce morbidity and mortality of heart failure patients in addition to guideline recommended pharmacotherapy.

Contents

Introduction

Coenzyme Q10 (also known as ubiquinone) was discovered by Crane et al. in 1957 in beef heart mitochondria [1]. It is the only endogenously synthesized lipid (by the mevalonate pathway) with a redox function which exhibits broad tissue and intracellular distribution in mammals [2]. However, endogenous synthesis of coenzyme Q10 declines with age [3]. Low CoQ10 (coenzyme Q10) levels can be efficiently corrected by exogenous supplementation.

Beneficial effects of CoenzymeQ10 supplementation were observed in some age-related diseases, for example metabolic syndrome, cardiovascular diseases, diabetes [4,5].

Coenzyme Q10 (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone) is synthesized by conjugating a benzoquinone ring with a hydrophobic isoprenoid chain of various chain length (Fig. 1) [1,6,7].

Coenzyme Q10 has two main functions:

1. an electron carrier in the mitochondrial respiratory chain (Fig. 2)
2. an antioxidant for lipid membranes.

Therefore, the effect of CoQ10 in cardiovascular diseases include [8,9]:

- positive influence on cardiac bioenergetics,
- scavenging free radicals and acting as an antioxidant,
- protective effect on endothelial cells,
- membrane stabilizer which interacts with phospholipids and proteins,
- positive influence on myocardial Na^+-K^+ ATPase activity and calcium channels,
- counteracting the “leak” of electrons in mitochondria,
- positive effect on DT-diaphorase,
- influence on prostaglandin metabolism,
- antiviscosity effect
- upregulation of genes especially those concerned with energy production

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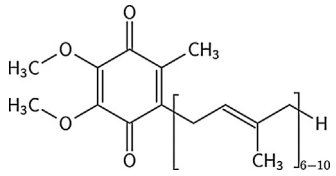

Fig. 1. Chemical structure of Coenzyme Q10.

Coenzyme Q10–pharmacokinetics and pharmacodynamics

Coenzyme Q10 plays a key role in oxidative phosphorylation and thus ATP production. Being an electron carrier, it transports electrons between complex I (NADH coenzyme Q reductase) and complex III (cytochrome bc1 complex) or complex II (succinate dehydrogenase) and complex III (Fig. 2). Therefore, it is vital for energy production processes in the heart [10].

Heart's demand of energy is reflected with large number of mitochondria. Greatest amounts of CoQ10 are presented mostly in the mitochondrion inner membrane. However, it can be also found in other membranous cell organelles, such as lysosomes, endoplasmic reticulum, peroxisomes, and vesicles [10].

Ubiquinol (reduced form, $CoQ10H_2$), protects membrane lipids from peroxidation. It also contributes to regeneration of vitamin E by reduction of alpha-tocopheroxyl radical.

Supplementing with exogenous CoQ10 was found to elevate the ubiquinol concentration in LDL subfraction therefore preventing their peroxidability [11].

Despite being a lipophilic compound, CoQ10 preparations often have low bioavailability. Lower bioavailability of CoQ10 could be associated with its hydrophobicity, large molecular weight (863 Da), and thermolability [12]. CoQ10 has two forms – ubiquinol and ubiquinone, with ubiquinol having higher bioavailability [13]. Different CoQ10 bioavailability is provided using various pharmaceutical forms (powder, suspension, oil solution, or solubilized form). Solubilized CoQ10 is preferred because of better absorption and higher plasma concentration, resulting in improved bioavailability (3–6 times higher compared to powder) which translate into its high cardioprotective effect (an increase in plasma and myocardium CoQ10 concentration) [1,13,14]. Table 1 summarizes a few trials using various pharmaceutical forms of CoQ10.

More studies have been carried out to improve the oral absorption of CoQ10 using oil solution and suspension system, lipid and surfactant based emulsion, solid dispersion system, self-emulsifying or self-microemulsifying drug delivery systems (SEDDS and SMEDDDS) and nanoemulsion [15].

The hydrophobicity of CoQ10 can be decreased using various methods of emulsification with modified food starch lecithin, gum arabic, polysorbate 80, or including γ-cyclodextrin. However, soft gelatin capsules containing soya bean oil suspension of CoQ10 have the highest bioavailability compared to those having polysorbate or lecithin as additives.

Greater bioavailability of CoQ10 can be obtained if it is taken with meals, because of the action of secreted bile acids [1,16–19].

According to the study of Nanjwade et al., nanostructured lipid formulation of CoQ10 has more antioxidant activity than solution [20].

Several human studies reported that it was necessary to use very high daily doses (300–3000 mg/day) of CoQ10 for long periods of time (even months) to observe any significant pharmacological or therapeutic effect. As a result, the amounts needed to provide protection from ROS (Reactive Oxygen Species) were very high [21–23]. It should be noted that supplementation does not significantly suppress the endogenous synthesis of CoQ10 and plasma CoQ10 concentration returns to initial value two weeks after the end of supplementation [13,24].

It was revealed in animal model that 14C-labeled CoQ10 administered intravenously resulted in increased radioactivity in the mitochondria inner membranes for at least 22 days. Oral administration provided similar results [16]. It was found that patients with myocardial failure had significantly decreased CoQ10 levels in blood and endomyocardial biopsies. The decrease correlated with severity of the symptoms [25]. Other studies can be consider as a clinical evidence demonstrating the uptake of oral Q10 into mitochondria, improvement in efficiency of mitochondrial energy production and increased contractility of myocardial tissue. These studies conclude that preoperative oral coenzyme Q10 therapy in patients undergoing cardiac surgery increases myocardial and cardiac mitochondrial coenzyme Q (10) levels, improves mitochondrial efficiency, and increases myocardial tolerance to *in vitro* hypoxia-reoxygenation stress [26,27].

Coenzyme Q10 and heart failure

Cardiovascular diseases represent a major health problem in the world. Only heart failure incidence approximates 10 per 1000 population after 65 years. The prevalence of heart failure is more than 23 million worldwide. The newest American data shows that approximately 5.7 million U.S. citizens ≥20 years of age suffer heart failure and it is anticipated to increase to 8 million people during the period 2012–2030 [28]. The incidence of heart failure increases with age. Mortality associated with heart failure was 284,388 in 2011, which is an increase compared to the data from 2009 (274,601). Similar trends can be observed in European population [28–30]. As a result new and efficient methods complementing the current treatment standard are continuously sought. Numerous publications indicated that Co Q10 had high

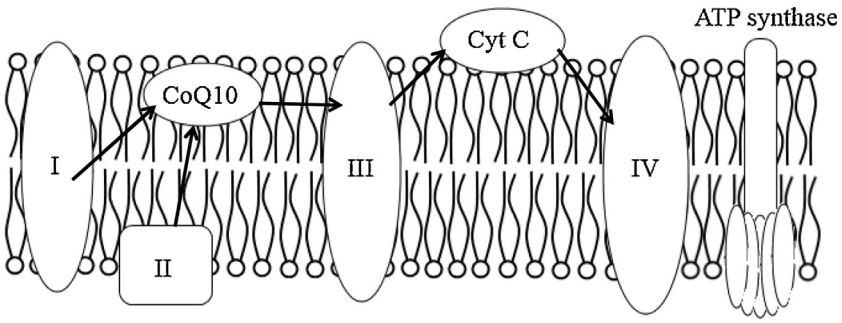

Fig. 2. Coenzyme Q10 in electron transport chain. I – complex I (NADH Coenzyme Q reductase), II – complex II (succinate dehydrogenase), III – complex III (cytochrome bc1 complex), IV – complex IV (cytochrome c oxidase), CoQ10–Coenzyme Q10, Cyt C – cytochrome C.

Table 1
Plasma CoQ10 concentrations after supplementation with different formulations of CoQ10 [11,43,63–65].

Trials	Forms of CoQ10	Dose (mg)	Duration	Plasma CoQ10 (μmol/L)	
				baseline	final
Chopra et al. [67]	susp.	120	21 days	0.50	1.37
	tabl.	120	21 days	0.52	1.60
	softgel caps.	120	21 days	0.50	3.31
Zita et al. [68]	oil susp.	30	2 months	1.355	1.992
	oil susp.	100	2 months	1.355	2.930
Rosenfeldt et al. [69]	oil susp.	300	2 weeks	0.452	1.842
Belardinelli et al. [48]	oil susp.	300	4 weeks	0.950	3.764
Hosoe et al. [13]	soft gelatin capsules	90	4 weeks	0.57	2.84
	soft gelatin capsules	150	4 weeks	0.65	3.84
	soft gelatin capsules	300	4 weeks	0.66	7.28

therapeutic potential in cardiovascular diseases [31–34]. For the first time CoQ10 was successfully used in heart failure in 1967 by YuichiYamamura [35]. Because of its poor prognosis, chronic heart failure represents a major public health problem all over the world. This clinical condition is usually associated with depletion of energy and low tissue CoQ10 levels [8]. Folkers et al. revealed that CoQ10) levels in blood and human endomyocardial biopsies were significantly decreased in patients with heart failure (the decrease correlated with severity of the symptoms: patients with dilated cardiomyopathy in NYHA Classes III and IV had lower tissue CoQ10 content than those of Classes I and II). Supplementation with CoQ10 (100 mg per 24 h) was beneficial for 69% and 43% of patients with cardiomyopathy and ischaemic heart disease, respectively. CoQ10 level in biopsy samples increased by 20%–85% after 2–8 months of supplementation [25].

The CoQ10 myocardial tissue levels in CHF patients were averagely 33% lower than in controls. In case of severe CHF (NYHA classes III and IV) even lower levels of endogenous CoQ10 were observed. Probably, such patients may positively respond to CoQ10 supplementation. The possible usefulness of the CoQ10 in the treatment of CHF may be attributed to improve both ATP synthesis and myocardial contractility [8,36]. CoQ10 is also a scavenger of free radicals and therefore it can decrease oxidative stress, which has detrimental role in heart failure patients [37]. It was proven by Nakamura et al. that cells lacking CoQ10 can incorporate exogenous CoQ10 molecules into the mitochondria [38]. On the other hand, Crestanello et al. observed in experimental model that supplementation with CoQ10 has positive effect on cellular energetics. This indicates its potential use in prevention and treatment of cardiovascular diseases [39]. Additionally, in 1998, Vogt suggested that reduced energy reserve in cardiac muscle may contribute to the progression of heart failure [40].

Soja and Mortensen carried out a metaanalysis of controlled clinical trials concerning CoQ10 supplementation and heart disease published during the years 1986–1995. The authors reported statistical significance of few parameters (stroke volume (SV), cardiac output (CO), ejection fraction (EF), cardiac index (CI), end diastolic volume index (EDVI). The metaanalysis showed that CoQ10 has good potential as an adjunctive treatment of CHF [41].

In 2006 a new metaanalysis was published by Sander et al., concentrating on the effect of CoQ10 on ejection fraction and cardiac output. The metaanlysis clearly showed that patients supplemented with 60–200 mg/day of CoQ10 for 1 to 6 months had a significant (3.7%) net improvement in ejection fraction. Surprisingly, even better clinical effect on ejection fraction (6.74%) was observed in patients with idiopathic cardiomyopathy in NYHA class I–III, who did not receive ACEI and were supplemented with CoQ10. In the CoQ10-treated group, mean cardiac output (CO) increased an average of 0.28 L/min Sander et al. suggested that less injured cardiac muscle contributes to better response to CoQ10 supplementation. The authors also provided some possible explanations for the influence of CoQ10 on EF and CO, including reduced ATP synthesis due to lack of CoQ10, role of CoQ10 in reduction of reactive oxygen species (their increased level can be observed in HF patients) and reduction of total peripheral resistance [42]. In the most recent meta-analysis Fotino et al. confirmed benefits of CoQ10 supplementation in heart failure that caused a pooled mean net change/increase of 3.67% in the EF and decrease of −0.30 in the NYHA functional class. Surprisingly, significant improvement in EF was found in trials with treatment duration ≤12 weeks, trials using doses of CoQ10 ≤100 mg/day, trials recruiting patients with less severe CHF and studies published before 1994. However, aforementioned analyses were carried out using small number of studies and therefore should be treated with caution [43]. Baggio et al. in the study on 2664 patients with NYHA class II and III observed that 3-month supplementation with CoQ10 (50–150 mg/day) resulted in improvement of many clinical symptoms, inculding cyanosis, oedema, jugular reflux, pulmonary rales, dyspnea, sweating, subjective arrhythmia, insomnia. Additionaly, more than three symptoms improved in half of the patients [44]. The same clinical data suggests correlation between improvement in heart failure symptoms and reduction of pro-inflammatory cytokines (interleukin (IL)-6, tumour necrosis factor (TNF)-alpha and IL-10 [45].

Based on the opinion that endothelial and mitochondrial dysfunction contribute to coronary artery disease and heart failure, Yak-Ling Dai et al. carried out a randomized, double-blind, placebo-controlled trial on the effect of 8-week CoQ10 supplementation on brachial flow-mediated dilation (FMD) in patients with stable ischaemic LVSD [46]. The study revealed that patients who received supplementation had significantly increased plasma CoQ10 level, FMD and decreased LP ratio compared with controls. Additionally, reduced LP ratio was correlated significantly with increase in FMD. Beneficial effect of CoQ10 supplementation on artery FMD in heart failure patients with diabetes mellitus was also confirmed in some previous studies [47–51]. Obtained FMD improvement (1.51%) was clinically relevant, because even 1% increase in FMD may be followed by 10–25% reduction of cardiovascular risk [46]. However, only few studies evaluating the role of CoQ10 in end-stage of heart failure suggest complementing standard therapy with addition of CoQ10 [52].

Belardinelli et al. observed that supplementation with CoQ10 300 mg/day increased significantly its plasma levels, correlating with improved LV function in patients with ischemic heart failure who combined pharmacotherapy with exercise training.

An additional valuable observation made in this group of patients was to determine CoQ10 plasma level which resulted in significant improvement of hemodynamic parameters (the endothelium-dependent arterial relaxation, LV contractility) [48].

Desired plasma concentration of CoQ10 for beneficial effects in heart failure patients is questionable. According to Langsjoen, such effects are visible with CoQ10 level >2.5 μg/mL. Supplementation

with low oral doses of CoQ10 cannot provide this concentration, which can explain why CoQ10 was ineffective in improving LV function in studies using 100 mg daily dose [53]. In trials where the clinical efficacy of CoQ10 in patients with heart failure was not confirmed, the dosage used was not high enough to ensure the recommended range of therapeutic levels (>2.5 μg/mL) [54–56]. The need for greater daily doses of CoQ10 (200–300 mg) was confirmed by Belardinelli et al., who observed that 300 mg/day of oral CoQ10 increased plasma CoQ10 concentration to 3.25±1.5 μg/mL [48].

In previous publication Belardinelli et al. observed that contractile response improvement was greater in initially akinetic (+33%) and hypokinetic (+25%) than dyskinetic segments (+6%). Moreover, improvement in systolic wall thickening score index (SWTI) was correlated with plasma CoQ10 concentration (highest change was observed in patients witch plasma CoQ10 > 2.4 μg/mL) [57].

The researchers, based on other results, suggested two ways in which CoQ10 can influence bioactivity of nitric oxide due to its antioxidant activity: decrease of superoxide generation and interaction with superoxide generation. Additionally, supplementation with CoQ10 can upregulate guanylyl cyclase, which is activated by binding nitric oxide. Heart failure is strongly associated with oxidative stress, which leads to increased production of peroxynitrite from nitric oxide (reacting with superoxide). CoQ10 reduces the rate of this reaction, therefore improving functional capacity. Contractile function is also upregulated by CoQ10, therefore improving metabolism and functioning of post-ischemic stunned cells and reducing left ventricular dysfunction [9,53,58].

Some studies indicate that CoQ10 may play a role as a marker of rejection in patients who underwent heart transplantation: low concentration of CoQ10 in plasma and endomyocardial biopsies was associated with histological signs of rejection while in patients without rejection signs CoQ10 level was within normal range. It is postulated, that supplementation of such patients with exogenous CoQ10 might contribute to prevention of transplant rejection [59,60].

Despite clinical efficiency, the role of CoQ10 as a predictor of mortality in chronic heart failure is not established by currently available data which provide divergent evidence. Molyneux et al. confirmed the role of plasma CoQ10 concentration as an independent predictor of mortality in patients with chronic heart failure. However, McMurrey et al. in a substudy of the Corona trial did not confirm it in a multivariable analysis though mortality was significantly higher among patients in the lowest compared to the highest CoQ10 tertile [61,62].Despite of this divergences, Mortensen et al. had designed “Q-symbio” trial to test the hypothesis that CoQ10 may reduce cardiovascular morbidity and mortality and ultimately establish its role in patients with chronic heart failure. “Q-symbio” was the first randomized double-blinded placebo controlled clinical trial with adequate power to address the efficacy of CoQ10 on morbidity and mortality of heart failure (420 patients with NYHA class III and IV). Recently published results of the trial clearly demonstrated that daily 300 mg of CoQ10 significantly reduced the risk of MACE (major adverse cardiac event): 30 (15%) patients in the group receiving CoQ10 reached the primary endpoint compared with 57 (26%) patients in the placebo group during 2-year follow-up. CoQ10 also decreased by 50% the risk of dying from all causes, which occurred in 21 (10%) patients in the CoQ10 group compared with 39 (18%) patients in the placebo group. All these benefits of CoQ10 were in addition to those afforded by β-blockers and ACEI or ARBs [63,64].

Thus, CoQ10 appears to be the first medication to improve survival in chronic heart failure since ACE inhibitors and β-blockers more than a decade ago. Moreover, supplementation with CoQ10 is well tolerated (up to daily 3600 mg; Hyson et al., 2010), with very low incidence of insignificant adverse effects. However, current guidelines do not recommend the use of CoQ10 in standard therapy of heart failure [30,44,65,66]. Results of many studies, especially including Q-Symbio, seem to be sufficient prerequisite for recommending CoQ10 in heart failure treatment.

Conflicts of interest

The authors declare no conflict of interest.

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