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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.

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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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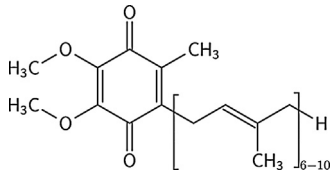

Fig. 1. Chemical structure of Coenzyme Q10.

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

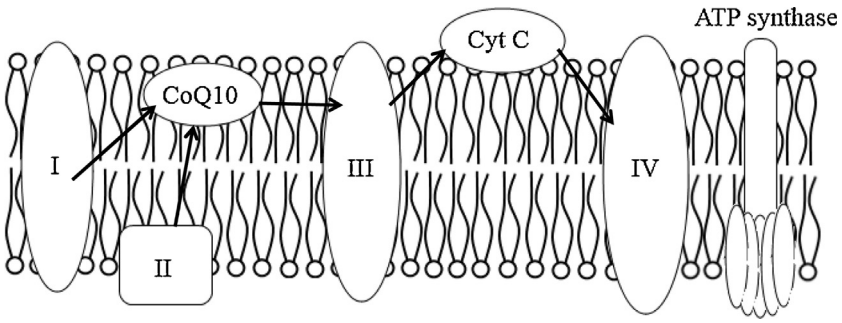

Fig. 2. Coenzyme Q10 in electron transport chain. I – complex I (NADH Coenzyme Q reductase), II – complex II (succinate dehydrogenase), III – complex III (cytochrome bc1 complex), IV – complex IV (cytochrome c oxidase), CoQ10–Coenzyme Q10, Cyt C – cytochrome C.