Cardiovascular Effects of Coenzyme Q10

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ABSTRACT

The prevalence of cardiovascular diseases is increasing year by year. In spite of the improvements that have been achieved in the medical management of the diseases, it is necessary to enhance the methods in some areas in order to prevent and manage these conditions more efficiently. To reach this goal, the prescription of supplements beside the conventional medications is a strategy which could be considered.

Coenzyme Q10 is an agent which is crucial for the production of ATP. With regard to its biological mechanisms, it is assumed that the administration of the agent may have beneficial effects on cardio-metabolic disorders. In this review, we aimed to review the advantageous effects of the agent on cardiovascular diseases.

Keywords: Coenzyme Q10; Review; Therapy; Reactive oxygen species; Antioxidant; Anti-inflammatory

BACKGROUND

Coenzyme Q was firstly discovered by Frederick Crane and his team, in 1957 [1]. The most common form of humane Coenzyme Q is believed to be Coenzyme Q10 (CoQ10), which acts as a cofactor in oxidative phosphorylation of adenosine triphosphate (ATP). In the oxidative phosphorylation process, CoQ10 might be oxidized (Ubiquinone) or reduced (Ubiquinol) [2]. Cellular bioenergetics depends on the appropriate activation of these cofactors, that has led to clinical usage of them in problems involving tissues with high metabolic needs, such as heart muscle [3]. The agent also has anti-inflammatory impacts as it suppresses the expression of tumor necrosis factor alpha (TNF-α) gene [4]. In addition, CoQ10 is an antioxidant, and reduces reactive oxygen species (ROS) [3,5]. The agent has similarities with vitamins, however, it shouldn’t be categorized as vitamin, because the body produces CoQ10 [3].

The effect of CoQ10 on the cardiovascular system was understudy since the discovery of the agent. Previous studies showed that CoQ10 deficiency could be present in variety of cardiovascular disorders such as mitral valve disease, aortic valve disease, cardiomyopathies, congenital valvular defects, ischemic heart disease, and myocardial infarction [6,7]. CoQ10 concentration was lower in the myocardium of patients with heart failure [8]. Also, CoQ10 levels are lower in smoker subjects and patients who suffer from hyperlipidemia [9]. While, it has been mentioned that CoQ10 concentration could not be used as a sole indicator of cardiovascular diseases [6]. Previous reports also showed that the administration of CoQ10 could be helpful in both prevention and treatment of cardiovascular diseases [7].

The published evidence showed that CoQ10 supplementation could have several therapeutic effects for diseases of different organs because of its anti-inflammatory and anti-oxidative properties. In the present study we aimed to review the beneficial impacts of CoQ10 on cardiovascular diseases.

ATHEROSCLEROSIS

Atherosclerosis is defined as the collection of lipid and cholesterol sediments within the sub-endothelial space of arteries leading to chronic inflammation [10]. Atherosclerotic cardiovascular disease is among the main causes of death, worldwide [3,11].

The immune system and inflammatory response play a decisive role in initiation and progression of atherosclerotic changes, that the condition could be classified into inflammatory diseases.
CoQ10 supplementation in apo-lipoprotein E deficient mice fed with a high-fat diet resulted in improvement of atherosclerotic lesions [18]. Other studies on animal models showed same results, since the CoQ10 had a preventing role on induction of atherosclerosis in mice [19]. A controlled, double-blind, randomized trial showed that CoQ10 with a dosage of 120 mg daily combined with aged garlic extract could improve the inflammatory markers of coronary atherosclerosis, and slow down the disease progression [20].

HYPERTENSION

Hypertension is considered as one of the leading preventable causes of cardiovascular disease [21]. In 2010, more than third of world adult population had been diagnosed with hypertension [22]. Nitric oxide (NO) plays a key role in blood pressure control, as it modulates central nervous system, and increases the endothelium capacity [23,24]. On the other hand, superoxide radicals can develop hypertension, because they react with endothelial NO and decrease bioavailability of NO [25].

There is evidence both in laboratory and clinical studies that shows the hypotensive effects of CoQ10 [26]. CoQ10 reduces peripheral vascular resistant which might be related to its ability of indirect increasing of endothelial NO by reducing oxidative stress [6,7,18,27]. It has been mentioned that CoQ10 administration decrease the need for other antihypertensive drugs [6,7].

Animal and human studies have shown CoQ10 supplementation could lower blood pressure [6]. A meta-analysis that included twelve trials demonstrated a reduction in systolic/diastolic blood pressure by 17/10 mm Hg without any significant side effects [28]. The recommended dosages to achieve this effect were between 34 mg/d to 360 mg/d in different studies [28]. However, a recent randomized, double-blind study on thirty patients showed contradictory results, since CoQ10 did not reduce systolic blood pressure, diastolic blood pressure, or heart rate in the patients [29].

CORONARY ARTERY DISEASE

Coronary Artery Disease (CAD) is a common form of cardiovascular diseases, and is considered among the most prevalent diseases, globally [30]. According to World Health Organization (WHO) published data, within 17.9 million of general population lose their lives due to CAD, worldwide, annually (31% of all deaths worldwide) [31].

Oxidative stress and inflammation are the key elements in development of CAD [32]. CoQ10 is an intracellular antioxidant which can protect mitochondrial membrane protein, and the membrane phospholipids from free radical-induced oxidative harm [33]. It is believed that CoQ10 might reduce CAD development because of its anti-oxidative and anti-inflammatory effects [34]. Many preclinical studies demonstrated the benefits of CoQ10 in pre/post-treatment of cardiac arrest, while more clinical evidence is needed to provide comprehensive results [6,26].

Previous studies mentioned that the high plasma level of CoQ10 is related with lower chance of CAD development [34]. CoQ10 could increase post-ischemic recovery in trabeculae of patients who underwent cardiac surgery [35]. Increased treadmill exercise tolerance with less ST-segment depression, decrease of angina frequency, and reduction in nitroglycerin use were noted in patients with stable angina after using CoQ10 supplements [6,7,26]. Moreover, the investigations on patients with acute coronary syndrome showed that CoQ10 supplementation improved anginal pain scores, left ventricular dysfunction, and arrhythmia [36-38]. Besides, CoQ10 lowered blood viscosity in ischemic heart disease patients [7]. Furthermore, a randomized, placebo-controlled study revealed that CoQ10 supplementation (300 mg/day) improves antioxidant enzymes activities and reduce inflammation in patients suffering from CAD [39].

MYOCARDIAL INFARCTION

Myocardial infarction (MI) is a medical condition that can lead to considerable rates of morbidity and mortality. MI could be among the first manifestations of CAD, or it might happen, recurrently, in cases with the diagnosed disease [40]. It is believed that the prescription of CoQ10 could be beneficial in patient with MI, and the underlying mechanisms are assumed to be the improvement of mitochondrial dysfunction and mitigation of DNA damage by anti-oxidative effect of the agent [41].

Animal models of MI which supplied with CoQ10 showed less severity of degeneration and necrosis of myocardium, aside from accelerated recovery [6]. Improved systolic function and infarct size reduction were observed due to infusion of CoQ10 after in rat models of acute myocardial infarction, as well [42,43]. In a study of 55 patients with ST elevation myocardial infarction, it has been shown that patients having higher plasma CoQ10 concentration 1 month after primary angioplasty had better left ventricle systolic function at 6-month follow-up [41]. Administration of CoQ10 in patients with acute myocardial infarction also improved angina, arrhythmia, and left ventricular dysfunction [6]. A randomized, double-blind, placebo-controlled trial on diabetic patients with the stable myocardial infarction showed that CoQ10 intake with dosage of 100 mg/day for 8 weeks, reduced the level of interleukin-6 (IL-6), and protein carbonyl [44,45].

CONGESTIVE HEART FAILURE

Heart Failure (HF) is a mixed clinical syndrome diagnosed with reduction of ejection capacity and impaired cardiac output, which occurs among millions of people, annually [46]. Year by year, the rate of new cases who are diagnosed with HF increases, resulting in high rates of morbidity and mortality [47,48]. Previous investigations showed that the plasma levels of CoQ10 can be considered as a negative predictor of the mortality in heart failure patients [8]. Lowered IL-6 and TNF-a were also seen in the heart failure patients who received CoQ10 supplementation [7]. CoQ10 supplementation improves mitochondrial and endothelial functions that could increase the survival and decrease the symptoms of HF patients [49-51]. Moreover, it is also mentioned that CoQ10 can protect the myocardium against ischemia [52].

CoQ10 supplementation could ameliorate cardiac output, which means that they can enhance cardiac contractility [53]. The subjective data, and the symptoms of heart failure such as cyanosis, rales, dyspnea, palpitation, jugular reflux, hepatomegaly,
sweating, insomnia, vertigo, and nocturia were also improved after the supplementation [6,7]. Supplemental treatment with CoQ10 in patients with congestive heart failure elevated stroke volume, Ejection Fraction (EF), cardiac output, cardiac index and diastolic volume index [54,55]. Moreover, the patients receiving CoQ10 demonstrated fewer complications and hospitalization [6]. In a more recent study, patients with moderate to severe HF received CoQ10 with dosage of 100 mg three times daily showed an enhancement of New York Heart Association (NYHA) functional classification, and 6-min walk test [56]. Consistently to these results, a recent meta-analysis, consisting of 2149 patients showed that the heart failure patients who received CoQ10 had higher exercise tolerance improvement, and lower mortality rate [57].

**CARDIOMYOPATHY**

Cardiomyopathies are disorders of heart muscle causing mechanical or electrical dysfunction, which can result in death and lowered quality of life [58]. They are classified to three general groups of dilated cardiomyopathy, hypertrophic cardiomyopathy, and restrictive cardiomyopathies [59]. Unfortunately, the rate of diagnosed cases is increasing year by year [60].

Studies have shown that the disease could be the result of high oxidative stress [61]. Hence over, CoQ10 is liable due to its role as an antioxidant [3].

The investigations on animal models of cardiomyopathy showed that CoQ10 can reduce fibrosis, left ventricular dysfunction, pro-inflammatory mediators, and cardiomyocyte hypertrophy [62,63]. Patients with dilated cardiomyopathy who received CoQ10 showed improvement in EF [7]. Moreover, 200 mg/day of CoQ10 supplementation in patients with hypertrophic cardiomyopathy enhanced NYHA class, quality of life, mitral regurgitation, 6-minute walk test, and diastolic dysfunction [7]. A double-blind, placebo-controlled prospective trial on children with dilated cardiomyopathy concluded that receiving CoQ10 with dosage of 2 mg/kg/day enhances diastolic function, and reduces chance of developing heart failure [64]. Animal studies and clinical trials demonstrated CoQ10 may prevent drug-induced cardiomyopathy by cardiotoxic agents including Adriamycin, Doxorubicin, and other Anthracyclines [6,7,26].

**METABOLIC SYNDROME**

The metabolic syndrome is generally occurred with an underlying cause of central obesity, insulin resistance, atherogenic dyslipidemia and systemic hypertension [65]. The condition is related with higher chance of atherosclerosis development as a result of vascular endothelial dysfunction, and chronic inflammation, and could increase the risk of CVD, as well [65].

CoQ10 capability of elevating serum insulin, improving endothelial dysfunction, lowering blood pressure suggests that it can be a therapeutic administration, decreasing the cardiovascular risk in metabolic syndrome [66].

Lowered levels of ubiquinone were observed in the renal cortex and mitochondria of diabetic mice models, which were associated with the higher rates of diabetic nephropathy and mortality [67,68]. In a randomized trial, 8 weeks of daily intake of CoQ10 supplement (100 mg/d) amid patients with metabolic syndrome resulted in improved serum insulin levels [69]. This might be because of the effects of CoQ10 on modulating insulin and adiponectin [70]. However, a meta-analysis, consisting of 7 trials, showed that receiving CoQ10 did not improve lipid profile, blood sugar level, and blood pressure in diabetic patients, while it lowered the level of triglycerides [71].

**ARRHYTHMIAS**

Patient with heart failure can develop atrial fibrillation which might lead to a rise in morbidity and mortality [72]. In fact, arrhythmias can raise the risk of myocardial infarction and hospitalization of patients with heart failure [73, 74]. Despite of some treatment methods for the disease which can improve the prognosis, there is still disagreement about the most effective management strategy.

Regular heart beat requires energy and as mentioned, CoQ10 has a major role in generation of ATP; therefore it is essential for normal pulse [75]. Furthermore, it is implicated that its effect could be related to lowering levels of malondialdehyde which may attenuate the incidence of atrial fibrillation (AF) [76]. Besides, the drug can reduce the inflammation and oxidative stress that are related to development of arrhythmias [77,78].

A randomized controlled clinical trial showed that 12 months treatment with CoQ10 with dosage of 30 mg/d, in patients diagnosed with heart failure, reduced the incidence of AF [76]. In addition, patients with ventricular premature beats (VPB) benefited from CoQ10 supplementation [7]. Moreover, CoQ10 administration in patients with acute myocardial infarction prevents QT-interval prolongation [7].

**CARDIAC SURGERY**

Cardiac surgery is a procedure which is performed widely around the world [79]. In spite of many efforts to improve the safety of this procedure, it is still considered as high-risk surgery with postoperative complications [80].

Inflammatory and oxidative stress responses to surgery are among postoperative consequences [81]. Indeed, the massive production of reactive oxygen species during the procedure has impacts on the endogenous antioxidant defense pool [82]. These consequences elevate the risk of organs damage during and after cardiac surgeries. For example, MI, respiratory failure, acute kidney injury could be happened after the surgery because of high oxidative stress [83]. Therefore, it is necessary to recover antioxidant enzyme activities before and after operations [83].

Clinical trials showed beneficial effects of CoQ10 in the setting of cardiothoracic surgery [26]. Administration of CoQ10 prior to cardiac surgery for 2 weeks resulted in better post-operative status, improved contractile function, and increased mitochondrial energy production, besides it also increased myocardial tolerance to in vitro hypoxia-re-oxygenation stress [53]. In a randomized double-blind clinical trial, patients who underwent CABG or valve surgery and received CoQ10 (100 mg 3 times a day) for at least two weeks had lower myocardial damage, enhanced redox state, and decreased duration of postoperative hospitalization [84]. However, an investigation showed that four weeks treatment with CoQ10 in the animal models that underwent CABG did not enhance the contractile reserve, and also did not reduce oxidative stress in the mitochondria (Table 1) [85].
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**Notes:** ROS: Reactive Oxygen Species; NO: Nitric Oxide; LDL: Low-Density Lipoproteins; EF: Ejection Fraction; VLDL: Very Low Density Lipoprotein
COQ10 AND HMG-COA REDUCTASES

Statins have a broad-spectrum usage in this era both in patients who have hyper-cholesteremia and patients with cardiovascular problems. These drugs reduce cardiovascular events in high-risk patients and patients with elevated low-density lipoproteins (LDL) [86]. Statins are usually well-tolerated and safe; however, they can produce a variety of side effects such as muscle pain and aches, creatine kinase elevations, myalgia, muscle weakness, cramps, and rhabdomyolysis which are called statin-associated muscle symptoms (SAMS) [87]. Researchers discussed these side effects could be due to the reduction of the cholesterol content of skeletal muscle membranes; reduction in farnesyl pyrophosphate, an intermediary for the production of ubiquinone; and reduction of the levels of ubiquinone [88]. Since CoQ10 is vitally important for cellular energy production and mitochondrial function, the administration of agent may be helpful to ameliorate SAMS [3].

Both animal and clinical studies demonstrate that administration of statins decreases the CoQ10 levels in plasma, but the evidence is inconsistent to prove the same phenomenon in tissues [87,89-93]. The reduction of CoQ10 concentration in plasma during statin therapy could be due to reduction of LDL [92]. The depletion of CoQ10 is more significant with high-dosage of statins and in older patients [87]. Moreover, mitochondrial function may be impaired by statin therapy which could exacerbate by exercise that would relate to a reduction in CoQ10 level, but more confirmatory data is needed [92]. It is also noteworthy to mention that patients who received Simvastatin had a decrease in muscle ubiquinone concentration, while no reduction was seen with the administration of Atorvastatin [94]. According to another investigation, it should be also noted that although Pravastatin lowers CoQ10 level, it did not lead to recurrent cardiovascular events [95]. Furthermore, the side effects of statin therapy caused by reduction in CoQ10 level are questioned by a systematic review [92].

A recent animal study conducted by Choi and his team showed CoQ10 treatment could reverse the statin-induced myopathy; besides, it has a synergistic effect with the drug in increasing high-density lipoprotein-cholesterol (HDLC) component [96]. In a clinical trial, CoQ10 treatment helps patients who showed worsening of diastolic parameters by receiving Atorvastatin [97]. A study in patients under statin therapy with myopathic symptoms demonstrated beneficial effects CoQ10 supplementation (with dosage of 100 mg/day) as it decreases pain severity after 30 days [98]; although, another 12 weeks pilot study in patients receiving Simvastatin did not show any beneficial effects of using oral CoQ10 (200 mg/day) in reducing myalgic pain [99]. Skarlavnik et al. demonstrated CoQ10 supplementation (50 mg twice daily) significantly reduced mild-to-moderate muscular symptoms of statin-therapy [100-105].

CONCLUSION

According to the published literature, CoQ10 supplementation could be a feasible and safe administration for patients who suffer from cardiovascular diseases. This could reduce the need for conventional therapy, and also lower morbidity and mortality rates. However, more studies should be conducted in order to evaluate the most effective dosage in each condition. Finally, the pharmacokinetics and pharmacodynamics assessment is the scope that should not be overlooked.

REFERENCES


