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REVIEW ARTICLE

Coenzyme Q10 in Cardiovascular and Metabolic Diseases: Current State of the Problem

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A R T I C L E H I S T O R Y

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Abstract: The burden of cardiovascular and metabolic diseases is increasing with every year. Although the management of these conditions has improved greatly over the years, it is still far from perfect. With all of this in mind, there is a need for new methods of prophylaxis and treatment. Coenzyme Q_{10} (CoQ_{10}) is an essential compound of the human body. There is growing evidence that CoQ_{10} is tightly linked to cardiometabolic disorders. Its supplementation can be useful in a variety of chronic and acute disorders. This review analyses the role of CoQ_{10} in hypertension, ischemic heart disease, myocardial infarction, heart failure, viral myocarditis, cardiomyopathies, cardiac toxicity, dyslipidemia, obesity, type 2 diabetes mellitus, metabolic syndrome, cardiac procedures and resuscitation.

Keywords: Coenzyme Q_{10}, hypertension, ischemic heart disease, myocardial infarction, heart failure, viral myocarditis, cardiomyopathies, cardiac toxicity, dyslipidemia, obesity, type 2 diabetes mellitus, metabolic syndrome, cardiac procedures and resuscitation.

1. INTRODUCTION

Coenzyme Q_{10} (CoQ_{10}) is an essential compound of the human body which is synthesized in the mitochondrial inner membrane [1]. The molecule of CoQ_{10} has a highly lipophilic character and the base of its structure belongs to quinone chemical group (Fig. **1**). The 10 indicates the number of isoprenyl units, which determines its low polarity and allows its fast diffusion through mitochondrial membrane [2]. It should be taken into consideration that CoQ_{10} exists in 2 forms: oxidized (ubiquinone) and reduced (ubiquinol) [1].

CoQ_{10} has many important functions in human body. Firstly, it can be named the key-component of electron transport chain in mitochondria necessary for ATP production [3]. CoQ_{10} transfers electrons from complex 1 to complex 3. Besides that, it plays a role in the protons' transfer in the inner mitochondrial membrane. This process is called protonmotive Q-cycle [4]. Q-cycle is a series of consecutive reactions of oxidation and reduction of CoQ_{10}, between ubiquinone and ubiquinol forms, which leads to free movement of protons through the lipid bilayer, and in the case of mitochondria through the internal mitochondrial membrane. It should be noted that the Q-cycle is inseparably linked to the respiratory chain of electron transfer.

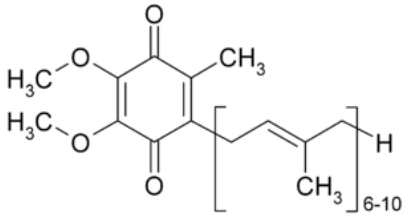

Fig. (1). CoQ_{10} formula.

In addition to its important role in electrons' transport, CoQ_{10} can act as an intercellular antioxidant, protecting the plasmatic membrane against peroxidation [5]. In a research, supplementation with CoQ_{10} showed an obvious decrease of the lipid hydroperoxides' concentration in atherosclerotic lesions in apolipoprotein E-deficient mice [6]. As a hydrogen

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Table 1. Distribution of Ubiquinone and Ubiquinol in tissues.

Organ	Ubiquinone Concentration (μg/g)	Ubiquinol Concentration (μg/g)	Effects	References
Heart	132.0	61.0	Antioxidant Bioenergetic Anti-inflammatory Membrane stabilizer Antiatherogenic	Aberg *et al*. [10] Miles *et al*. [11]
Kidneys	77.0	75.0		
Liver	63.6	95.0		
Muscle	39.7	65.0		
Brain	13.4	23.0		
Pancreas	32.7			
Spleen	24.6			
Lung	7.9	25.0		
Thyroidea	24.7			
Testis	10.5			
Intestine	11.5	95.0		
Colon	10.7			
Ventricle	11.8			
Plasma(μmol/ml)	1.1	96.0		

donor, it is more effective than other antioxidants. Besides that CoQ_{10} is able to regenerate the oxidized form of α-tocopherol [4]. We also have to mention that CoQ-dependent NADH-oxidase is a transporter of electrons across the plasma membrane. It plays role in cell growth and differentiation [7]. Likewise, the Q-cycle has generated ubisemiquinone which generates superoxide anion radical by means of reaction with molecular oxygen producing than hydrogen peroxide that influences redox state.

Due to its important place in organisms' functioning, there are many diseases and degenerative states associated with CoQ_{10}'s deficiency such as diabetes mellitus, cardiovascular disease (including atherosclerosis, hypertension, dyslipidemia), muscular dystrophy, Alzheimer's disease, Parkinson's disease and others [8].

Administration of selenium and CoQ10 in a group of healthy elderly participants given four years of intervention results in a significantly reduced cardiovascular mortality, which was observed for 10 years [9]. Therefore, this review is aimed to sum up the current possibilities to use CoQ_{10} in a variety of cardiovascular and metabolic conditions with an analysis of its impact on patients' health and quality of life.

2. FUNCTIONS OF CoQ_{10} IN HEART DISEASES

In the body, CoQ_{10} is found in all systems of organs (Table **1**). The highest concentration of ubiquinone is observed in the tissues of the heart, kidneys, liver and muscles. In its turn, in cells - in the vesicles of the Golgi apparatus, mitochondrial plasma membranes, lysosomes.

One of the main causes of death in the world is cardiovascular diseases. Oxidative stress is considered to be an essential player in the development of this group of diseases. In such a way, this leads to the theory that antioxidants' can lower the risk of cardiovascular disease [12].

Indeed, three out of four patients with heart diseases have low levels of CoQ_{10}. It was noticed that CoQ_{10}'s plasma levels in patients with ischemic heart disease and dilated cardiomyopathy are much lower than in healthy ones. Depending on the severity of heart injury circulating level of CoQ_{10} decreases in direct proportion to disease progression [13]. There are several theories about the role of CoQ_{10}'s mechanism of action in cardiovascular disease.

Firstly, because of its antioxidant effect as it was mentioned above. Ubiquinone should be reduced to ubiquinol to completely show its antioxidative function. It is known, that Reactive Oxygen Species (ROS) can cause serious cellular damage by means of reacting with cell membranes, DNA and protein centers [14]. Besides that, the products of oxidative stress and cytokines may lead to hypertrophy because they trigger the growth of myocytes [15, 16]. Ubiquinol or the reduced form of CoQ_{10} stops the initial process of lipid peroxyl radicals' formation. That is the reason why CoQ_{10} is considered to be a very potent antioxidant against ROS and free radicals in biological membranes [17].

Secondly, CoQ_{10} plays a great role in the heart's energetic needs. For example, the process of cardiac contraction, which involves the release of Ca^{2+} from the sarcoplasmic reticulum and the following activation of the contractile proteins requires energy [18]. There is a theory that myocardial failure may be caused by the reduced production of the energy in mitochondria [13]. However, as it was mentioned before, CoQ_{10} is the main component in the transport of electrons necessary for ATP production.

Besides that, we should mention anti-inflammatory effect, because different cardiovascular diseases, for example, heart failure are related to chronic pro-inflammatory state, supposing increased circulating levels of cytokines and adhesion molecules [19]. There are some new studies that establish anti-inflammatory properties of CoQ_{10} possibly by means of nitric oxide's regulation, and that mechanism may be effective in heart failure treatment [20, 21]. Thus, the cytokines' and chemokines' secretion wouldn't induce myocardial fibrosis and lead to Heart Failure (HF) development [22]. The main effects of CoQ_{10} administration in different conditions are presented in Table **2**.

3. CoQ_{10} AND HYPERTENSION

Nowadays, hypertension is one of the major causes of morbidity and mortality worldwide. In 2010, the global prevalence of hypertension was 31% of all adults or 1.39 billion people. Therefore, between 2000 and 2010, there has been an increase of 5.2% in global hypertension prevalence. An interesting fact is that in high-income countries, the number of patients with hypertension decreased by 2.6 % but low-income ones increased by 9.9 % [23]. It is important to mention that nitric oxide and reactive oxygen species play a significant role in the regulation of blood pressure by means of modulation of the central nervous system [24]. It is known that increased generation of reactive oxygen species and lack of bioavailability of nitric oxygen activate hypertensions' neurogenic pathogenesis [25].

One of the possible mechanisms for the hypertension development is the superoxide radicals' production caused by oxidative stress. Superoxide radicals promptly enter in reaction with endothelial nitric oxide and produce peroxynitrite. In such a way, the bioavailability of nitric oxide decreases [26]. At the same time with the nitric oxides' decrease, the capacity of endothelium to relax underlying smooth muscle disappears and this leads to vasoconstriction and subsequent blood pressure increase. CoQ_{10} in its turn by means of a direct effect on the endothelium provokes vasodilation and lowering of blood pressure [27, 28]. It should be mentioned that though CoQ_{10} sustains nitric oxides' bioavailability and induces vasodilatation in a patient with hypertension, in healthy people it doesn't have a vasodilatation effect.

It is considered that CoQ_{10} adjusts the angiotensin effect in sodium retention and decreases the level of aldosterone [29]. This effect was proved in a study where CoQ_{10} was administrated as an adjuvant to usual antihypertensive therapy to keep serum level of CoQ_{10} equal to 2.0 μg/ml [30]. Finally, they got their results and noticed an improvement in functional and clinical condition in 6 months.

In a randomized, double-blind, placebo-controlled study, it was observed that after 12 -week of CoQ_{10} administration, the systolic blood pressure was lowered to normal limits [31]. In another systematic review [32], it was assumed that CoQ_{10} can lower the systolic blood pressure with 11 mm Hg and the diastolic one with 7 mm Hg. In addition, it should be mentioned that in patients with such diseases as type 2 diabetes mellitus and ischemic left ventricular systolic dysfunction, when the blood pressure is normal, administration of CoQ_{10} didn't modify the blood pressure [33-35]. In other words, the antihypertensive effect of CoQ_{10} is limited only to patients with hypertension and does not decrease systemic pressure in patients without hypertension.

4. ISCHEMIC HEART DISEASE

There are reports that some ethnical groups are more susceptible to ischemic heart disease, possibly due to lower levels of CoQ_{10}. For example, it was noticed that in Indian males, the plasma level of CoQ_{10} is considerately lower than

Table 2. CoQ_{10} administration in different conditions.

Condition	Possible Effects	References
Hypertension	Scavenging of ROS Vasodilatation Angiotensin effect adjustment Aldosterone level reducing	[27-29]
T2DM	Protection against ROS Antioxidant Fatty acid oxidation enhancement	[130-132]
Metabolic syndrome	Protection against ROS Antioxidant Tissue-protective The increase in triglyceride-rich lipoproteins (VLDL)	[115, 133]
Overall role in cardiovascular disease	Antioxidant Protection against ROS Bioenergetic Anti-inflammatory	[14, 18, 19]

the normal one. It was presumed that due to this fact, they are more susceptible to coronary heart disease [36]. On the contrary, there is the low frequency of ischemic heart disease in Greenlanders. In comparison with Danish population, the Greenlanders have higher serum level of CoQ_{10} = 1.495 nmol/ml (males) and 1.421 nmol/ml (females) ($p<0.001$). This may be because of the diet, which consists of fish and sea mammals [36].

A study was conducted in which patients with Coronary Artery Disease (CAD) to determine the effect of CoQ_{10} oral administration in dose 100 mg of the endothelium-dependent vasodilatation activity of extracellular superoxide dismutase (ecSOD). The results demonstrated that in CoQ_{10} treated group in comparison with placebo group: ecSOD, endothelium-dependent relaxation was statistically higher [37].

In another study, the amount of CoQ_{10} supplement administrated per day constituted 300 mg. After the beginning of CoQ_{10} supplementation, the extent of anti-inflammatory markers (TNF-α, $p=0.039$) was significantly lower. In comparison with the placebo group, the levels of vitamin E ($p=0.043$) and the antioxidant activities of enzymes ($p<0.05$) were remarkably higher after 12 weeks. Therefore, CoQ_{10} level in plasma had positive correlation with the antioxidant activity of enzymes ($p<0.05$) and vitamin E ($p=0.08$) and negative one with interleukin-6 (IL-6) ($p=0.027$) and TNF-α ($p=0.034$) [38]. On the other hand, the data shows no relationship between CoQ_{10} serum level and the severity of CAD in patients with angina pectoralis [39].

Lee and coworkers [40] concluded that CoQ_{10} plasma level may have a positive correlation with vitamin B status. In addition, the plasma level of vitamin B-6 and CoQ_{10} in patients with CAD is low. To be more precise, the risk for patients with CoQ_{10} plasma level ≥516.0 nmol/l (0.516 μmol/l) was lower. However, there is a need for further studies for a deep understanding of inter-influence of CoQ_{10}, vitamin B-6 and their coinfluence on CAD.

There are also studies that support a cardioprotective effect of CoQ_{10} where its plasma levels were compared with malondialdehyde level and antioxidant activities of the following enzymes: superoxide dismutase, catalase, glutathione peroxidase [41]. CoQ_{10} plasma level had a positive correlation with glutathione peroxidase and catalase and a negative one with malondialdehyde level and superoxide dismutase. Furthermore, CoQ_{10} administration (150 mg/per day) seems to reduce the IL-6 level in CAD patients. This fact demonstrates its anti-inflammatory properties [42]. It is well known that pro-inflammatory state is a major component of chronic disease and significantly influences their progression.

5. CoQ_{10} AND MYOCARDIAL INFARCTION

Cardiovascular diseases are the leading cause of death and were accounted for almost the third of all deaths globally in 2013 [43]. Several randomized studies demonstrated beneficial effects of CoQ_{10} in patients with Myocardial Infarction (MI). One of the studies showed a significant increase HDL-C level in serum. Besides the concentrations of intercellular adhesion molecule, 1 and IL-6 in serum were significantly decreased in CoQ_{10} group which underlines the metabolic and anti-inflammatory effects [44]. Another randomized study which involved diabetic patients with CAD supports the findings of the anti-inflammatory effect of CoQ_{10} although didn't find any improvement of cardiometabolic markers [45]. This may be due to the fact that patients with Type 2 Diabetes Mellitus (T2DM) represent a distinct group of patients with different underlying pathogenetic mechanisms for MI. Finally, another randomized study in patients with MI and hyperlipidemia demonstrated improvement of blood pressure, serum HDL-C as well as LDL-C/HDL-C and TC/HDL-C ratios [46]. Co-administration of CoQ_{10} and L-carnitine along with therapeutic lifestyle change may be a better alternative with a significant impact on the quality of life [47]. The protective effect of CoQ_{10} can be explained by its influence on coagulation. Administration of 100 mg of CoQ_{10} twice daily for 20 days led to a three-fold increase of total serum CoQ_{10} level with a decline in plasma fibronectin (-20.2%), thromboxane B2 (-20.6%), prostacyclin (-23.2%), and endothelin-1 (-17.9%) level as well as inhibition of vitronectin-receptor expression and reduction of platelet size [48, 49]. Animal models have shown similar results with mild antiaggregatory changes in the hemostatic profile [50].

Furthermore, patients with MI who had higher plasma CoQ_{10} concentrations 1 month after primary angioplasty had better left a ventricular performance at 6-months follow-up. In addition, higher plasma CoQ_{10} concentration was associated with lower grade inflammatory and oxidative stress status. The authors, therefore, proposed plasma CoQ_{10} concentration as a prognostic biomarker of left ventricular systolic function after revascularization therapy for MI [51].

Rat models demonstrate that CoQ_{10} injection intravenously 10 min after coronary artery occlusion results in a smaller area of the necrosis, less postinfarction hypertrophy of the left ventricle, greater stroke volume, stroke work, cardiac output, ejection fraction, and contractility, but lower end-diastolic pressure [52]. It seems to improve the survival of myocardial cells during ischemia and limit postinfarction myocardial remodeling [53]. It is important to emphasize that in this model, the plasma concentration of CoQ_{10} was by 87% or more than 2 times higher than in the control group of rats [52, 53].

6. CoQ_{10} AND HEART FAILURE

HF represents a composite clinical syndrome, which includes a decreased ejection capacity and disturbed cardiac output because of structural or functional disorders of the heart. Globally, every year, millions of people are diagnosed with HF [54]. Besides that, HF has become the most often reason for hospitalization and impairment [55, 56]. According to the statistics, despite the fact of pharmacological development and improvement, deaths from HF exceed 10% per year, but in some settings from 20% to 50% [57]. Oral administration of CoQ_{10} has been observed to raise the endogenous level of CoQ_{10} in plasma [58]. In agreement with studies, the plasma level of CoQ_{10} can be proposed as a predictor of the mortality in HF patients [59].

Besides the functions of CoQ_{10} mentioned before, one of the actions of CoQ_{10} in HF is the inotropic one. It improves cardiac output by the rise of heart's contractile force [60]. It

is supposed that CoQ_{10} improves the oxygen utilization on the cellular level.

In a randomized controlled multicenter trial that evaluated patients with HF that received 100 mg CoQ_{10} 3 times daily or placebo, in addition to standard therapy demonstrated lower cardiovascular mortality (9% vs. 16%, p=0.026), all-cause mortality (10% *vs*. 18%, p=0.018), and incidence of hospital stays for HF (p=0.033). In addition, a significant improvement of NYHA class was found in the CoQ_{10} group after 2 years (p=0.028) [61]. Another Q-Symbio trial demonstrated the inter-influence between CoQ_{10} and HF endpoints during 2 years CoQ_{10}/placebo administration. CoQ_{10} remarkably diminished the long-term endpoint (cardiovascular morbidity) in the group which administrated placebo (the adverse effect was noticed just in 15% patients *vs*. 26%, p=0.003) [62]. Generally, Q-Symbio studies showed that CoQ_{10} administration along with the standard therapy turned out to be well tolerated and useful in reducing cardiovascular adverse events and HF management [63]. However, the short-term endpoints (biomarker status, functional capacity and symptoms) in patients who administrated CoQ_{10} and placebo were almost the same.

The administration of CoQ_{10} in patients with HF awaiting heart transplant led to a significant improvement in functional status, clinical symptoms, and quality of life. However, there were no objective changes in echo measurements or atrial natriuretic factor and TNF blood levels [64]. A meta-analysis also showed that in HF patients supplementation with CoQ_{10} resulted in a pooled mean net change of 3.67% (95% CI: 1.60%, 5.74%) in the ejection fraction and -0.30 (95% CI: -0.66, 0.06) in the NYHA functional class [65].

Therefore, the conclusion was that the drugs which are used for HF treatment can't replace coenzymes or vitamins. Coenzymes' supplement is needed to increase the survival In HF. Weakened bioenergetics and lack of energy which are met in HF could be corrected by CoQ_{10} refill [66].

7. CoQ_{10} AND ARRHYTHMIAS

The prevalence of the Atrial Fibrillation (AF) and HF are growing worldwide year by year [67]. Atrial fibrillation can be called a typical atrial arrhythmia in patients diagnosed with HF. It is associated with an increase in morbidity and mortality [68, 69].

CoQ_{10} plays an important role in oxydative phosphorilation, producing ATP and this bioenergetic function is essential for proper heart functioning [70]. Besides that, it has the property to scavenge ROS and antioxidant function [71].

There are many risk factors in the AF development, including the inflammation associated with an increase in the level of circulating cytokines [72]. Besides that, oxidative stress contributes to the accumulation of ROS which depresses the cardiac function [73]. To reduce the inflammation, following drugs are used: angiotensin receptor blockers, statins and others [74].

In the study, it was concluded that the use of CoQ_{10} as adjuvant therapy to statins decreased the inflammation level and the levels of inflammatory cytokines. After 6 months of use, the influence on the AF wasn't shown [75].

A systematic review and meta-analysis of eight clinical trials found that patients with CoQ_{10} treatment were significantly less likely to require inotropic drugs after surgery [OR 95% Confidence Interval (CI) 0.47 (0.27-0.81)], and to develop ventricular arrhythmias after surgery [OR (95% CI) 0.05 (0.01-0.31)].

In a group of patients with HF, there was a significant reduction in the level of malondialdehyde in the CoQ_{10} group. Three patients (6.3%) in the CoQ_{10} group and 12 patients (22.2%) in the control group had episodes of AF after 12 months' treatment (p=0.02) [75]. Thus, it seems that it may have an antiarrhythmic effect.

8. VIRAL MYOCARDITIS

Mice models show that the survival rate is significantly higher in the group of mice with viral myocarditis that received CoQ_{10} than in the control group [76]. Histologic examination showed that the severity of myocarditis was less in the CoQ_{10} group. The inflammatory process induced by the virus was suppressed by the CoQ_{10} treatment. Thus, pretreatment with CoQ_{10} may reduce the severity of viral myocarditis in mice decreasing oxidative stress in the condition [77]. A study in humans demonstrated that there is a beneficial effect of CoQ_{10} and trimetazidine individually, but demonstrated a superior effect of combining the therapies on cardiac left ventricular ejection fraction, and biochemical markers of myocardial damage in acute viral myocarditis [78].

9. CARDIOMYOPATHY

Cardiomyopathy is a debilitating condition, which is associated with a high mortality and poor quality of life. There is extensive evidence from in vitro and animal studies that it is linked to increased oxidative stress [79].

Mice models of diabetic cardiomyopathy demonstrate that CoQ_{10} decreases diabetes-induced left ventricular diastolic dysfunction; cardiomyocyte hypertrophy, fibrosis and apoptosis; expression of the atrial natriuretic peptide, connective tissue growth factor, pro-inflammatory mediators, and β-myosin heavy chain [80, 81].

CoQ_{10} deficiency is frequently encountered in dilated cardiomyopathy and this may be reversible by the CoQ_{10} administration but the therapeutic effects depend on the basal plasmatic and myocardial levels [82]. It may even attenuate disease progression and preserved left the ventricular function in animal models [83]. In children with dilated cardiomyopathy, it may improve NYHA class, cardiothoracic ratio and shorten ventricular depolarization [84]. In a prospective, randomized, double-blinded, placebo-controlled trial in children with dilated cardiomyopathy, CoQ_{10} administration for 6 months resulted in improvement of diastolic function and a lower mean score for the index of cardiac failure [85].

In patients with hypertrophic cardiomyopathy that were treated with an average of 200 mg/day of CoQ_{10}. All patients noted improvement in symptoms of fatigue and dyspnea with no side effects noted. The mean interventricular septal thick-

ness and mean posterior wall thickness improved significantly. Mitral valve inflow slope by pulsed wave Doppler showed a non-significant trend towards improvement [86]. There is also a significant improvement in NYHA class, and quality of life [87].

10. CoQ_{10} AND CARDIOTOXICITY

The latest studies hypothesize the role of CoQ_{10} in cardiotoxicity, induced by some drugs.

One of the groups of drugs used in chemotherapy is anthracycline antibiotics. It is usually used in the treatment of hematological cancers: leukemias, lymphomas and in the solid malignancies: carcinomas, sarcomas. One of the strongest and the best-known side effects of anthracycline is cardiotoxicity [88].

Doxorubicin is used for the treatment of early-stage breast cancer. It is known to improve the overall survival. Nonetheless, some patients are likely to develop such side effect as cardiomyopathic disturbances and congestive heart failure. It is suggested that these disturbances may appear by virtue of raised ROS generation. It is known that CoQ_{10} protects mitochondria against ROS. In such a way, it could be introduced in adjuvant therapy to avoid doxorubicin's side effects. On the other hand, there is data that CoQ_{10} did not have any influence on doxorubicin cell toxicity thus there is a need for further studies [89].

Later, it was found, that CoQ_{10} and L-carnitine administration, started within 5 days before doxorubicin use, improved heart's functions, decreased Troponin-l, Troponin-T, IL-1 and TNF-α levels. It also showed a protection against oxidative stress by reducing levels of nitric oxide and malondialdehyde. Therefore, it seems that CoQ_{10} and L-carnitine administration together may protect the myocardium [90].

In addition, isoproterenol, which is an agonist of β-1and β-2 adrenergic receptors, can induce oxidative stress in the myocardium and produce infarct-like necrosis [91]. Furthermore, it influences on the lipid ratio in the myocardium and this fact can lead to CAD development [92]. Beside this, isoproterenol may stimulate lipid peroxidation and this way disturbs myocardial membrane [93]. CoQ_{10} pretreatment in a dose of 100 mg/kg for 18 days showed a protection against cardiac hypertrophy and cardiotoxicity and lowered lipid peroxidation in rats [94].

11. CoQ_{10} AND DYSLIPIDEMIA

The 3-hydroxy-3-methylglutaryl Coenzyme A (HMG-CoA) reductase inhibitors are frequently used for the treatment of conditions associated with high levels of circulating cholesterol. Besides, this group of drugs inhibits some antioxidant effectors [95, 96] and vasoactive nitric oxide [95-97]. It should be mentioned that the pathway of cholesterol' biosynthesis and CoQ_{10}' is similar (mevalonate pathway). Therefore, HMG-CoA reductase inhibitors block cholesterol synthesis and CoQ_{10} ones by reducing the level of farnesyl pyrophosphate [98]. The depletion of CoQ_{10} is really important in elderly because with time, the endogenous level of CoQ_{10} decreases [99].

Although, in general, statins are safe, the following most frequently occurring side effects were recorded. The most frequent musculoskeletal side effects of statins include increased levels of creatine kinase, myopathy, dermatomyositis, and rhabdomyolysis [100, 101]. Other disorders with the rarer frequency of the musculoskeletal system include arthralgia, myalgia and tendon rupture [102, 103]. In addition, one of the side effects is accelerated cataract progression.CoQ_{10} deficiency resulting from statin therapy can disrupt cellular energy metabolism and contribute to the development of myopathy and other muscle symptoms [104, 105]. Although a recent meta-analysis of five studies with 226 participants didn't support these findings. Though it is accurately noted that the human body contains about 2 g of CoQ_{10}, of which 500 mg must be replaced each day by diet and a supplement of one or two grams per day should be evaluated in the future [106, 107]. Finally, there are also other ways to manage statin intolerance [108].

Statins may lower the level of CoQ_{10} up to 40% by means of HMG-CoA reductase blocking. This effect is harmful to patients with heart failure [109]. That fact was proved in many clinical studies [98, 110-115]. In such a way, it was concluded that it is better to administrate CoQ_{10} supplementation simultaneously with statin therapy to avoid myopathic side effects. In the study of 103 patients, it was postulated that statins have a good effect and less side effects being used in combination with CoQ_{10} [116].

12. CoQ_{10}, TYPE 2 DIABETES AND METABOLIC SYNDROME

It is often observed that there is CoQ_{10} deficiency in patients with T2DM, their plasma level is much lower than in the healthy ones [117, 118]. This fact can lead to defensive mechanisms' decrease in conditions of strong oxidative stress, induced by hyperglycemia [119]. This led to the theory about attenuation of mitochondrial dysfunction by means of supplementation with CoQ_{10}. Thus leading to the idea that it can also influence the glycemia levels [120].

As it was mentioned before, there are two forms of CoQ_{10}: ubiquinone and ubiquinol. In the organism of healthy human, they are in a determined ratio to protect the organism from oxidative stress. Sometimes the ubiquinone-ubiquinol ratio is considered to be the marker of the oxidative stress [121]. Patients with T2DM have a deficiency of ubiquinol, which interacts with reactive species of oxygen and protects the organism. Besides that, the ubiquinone-ubiquinol ratio was much higher in a patient with T2DM after the breakfast and throughout the day, that suggests a heightened oxidative stress on the background of postprandial hyperglycemia [122].

An interesting theory was proposed by Sourris and coworkers, who considered that CoQ_{10} is a precipitating factor for diabetic nephropathy [119]. They explained it with that fact that the level of ubiquinone in the renal cortex and mitochondria in mice was low and was likely to produce diabetic nephropathy [123]. It should be noted that diabetic nephropathy is an important prognostic factor of mortality in patients with diabetes [124].

On the other hand, a recent systematic review and meta-analysis that included seven trials, involving 356 patients demonstrated that CoQ_{10} supplementation had no beneficial effects on glycemic control, lipid profile or blood pressure in patients with diabetes. However, it reduced triglycerides levels. This leads to a reasonable conclusion that there is a need for new well-designed randomized controlled trials that determine the effect of CoQ_{10} on metabolic profile in diabetes as well as an exploration of the dosage effects [125].

Interestingly in randomized trial patients with metabolic syndrome daily intake of 100 mg, CoQ_{10} supplements for 8 weeks had beneficial effects on serum insulin levels, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), Homeostatic Model Assessment of β-cell Function (HOMA-B) and plasma total antioxidant capacity concentrations [126]. This may also indicate that supplement of CoQ_{10} in patients with metabolic syndrome may be more beneficial than in patients with TDM. For instance, patients with polycystic ovary syndrome have the concomitant metabolic disease and randomized trials demonstrate that CoQ_{10} had beneficial effects on glucose metabolism, serum total- and LDL-cholesterol levels [127].

Finally, the management of T2DM as well as metabolic syndrome is a complex process and includes several drugs. For instance, in a rat model administration of metformin with CoQ_{10} showed a better renoprotective effect than CoQ_{10} or metformin alone [128]. This is also true for other drugs such as sitagliptin [129]. This brings up an important point that CoQ_{10} may potentiate the effects of other drugs by some mechanisms.

13. CARDIAC SURGERY AND PERCUTANEOUS CORONARY INTERVENTION

Cardiac procedures are tightly linked to oxidative stress. The extensive production of reactive oxygen species affects the endogenous antioxidant defense pool. The recovery of antioxidant enzyme activities may be a key goal during the pre- and postoperative periods [134].

Administration of CoQ_{10} increases its concentration in serum, atrial trabeculae, and isolated mitochondria. This results in a more efficient mitochondrial respiration (adenosine diphosphate/oxygen ratio) and decreased mitochondrial MDA content. After 30 minutes of hypoxia *in vitro*, pectinate trabeculae isolated from patients receiving CoQ_{10} exhibited a greater recovery of developed force compared with those in patients receiving placebo. This leads to the conclusion that preoperative oral CoQ_{10} therapy in patients undergoing cardiac surgery increases myocardial and cardiac mitochondrial CoQ_{10} levels, improves mitochondrial efficiency, and increases myocardial tolerance to in vitro hypoxia-reoxygenation stress [135].

On the other hand, in a swine models of hibernating myocardium with the daily CoQ_{10} administration of 10 mg/kg/day were evaluated with MRI at 4-week following Coronary Artery Bypass Graft Surgery (CABG). CoQ_{10} did not improve contractile reserve or reduce oxidant stress at 4-week post-CABG [136].

In a randomized trial, patients undergoing CABG and/or valve surgery received in double-blinded fashion, while on the waiting list for surgery and one month after surgery, either metabolic therapy (CoQ_{10}, magnesium orotate, lipoic acid, omega-3 fatty acids and selenium) or placebo. The results demonstrated improved redox status, reduced myocardial damage, and shortened length of postoperative hospital stay [137]. Although in this model, the patients received a group of substances and not only CoQ_{10}. Similar studies advocate for a more complex management of the patients, which should include metabolic (CoQ_{10}, alpha- lipoic acid, magnesium orotate and omega-3 fatty acids), physical and mental preparation before cardiac surgery that may improve quality of life, lower systolic blood pressure, reduce levels of oxidative stress and thus has the potential to enhance postoperative recovery [138].

There are also reports that patients who received CoQ_{10} had significantly fewer arrhythmias, lower total inotropic requirement, mediastinal drainage, blood product requirement, and shorter hospital stays [139-141].

Still, there are other studies that did not show improved myocardial protection in patients undergoing coronary revascularization although they were treated with 600 mg of CoQ_{10} 12 hours before the procedure [142].

Furthermore, the CoQ10 level may play a role in heart rejection after a transplant. CoQ_{10} level and mitochondrial bioenergetic functions of endomyocardial biopsies contribute to the explanation of pathobiochemical mechanisms of rejection thus CoQ_{10} therapy could contribute to the prevention of rejection of the transplanted heart [143]. Myocardial and blood CoQ_{10} concentrations are significantly decreased in the incipient phase of rejection (degree 0-1) and in rejection phase 1 and 2 [144].

Finally, during percutaneous transluminal coronary angioplasty, myocardial ischemia occurring during balloon inflation is brief and regresses completely after balloon deflation. Reperfusion following a short period of acute ischemia does not alter the CoQ_{10} levels and represents a mild oxidative stress [145]. In a randomized, clinical trial, the intervention group of 50 patients received a 300 mg loading dose CoQ_{10} 12 hours before the procedure. No significant change was reported in the level of cardiac biomarkers but there was a significant reduction in high sensitive C-reactive peptide level in CoQ_{10} group [146]. This supports the evidence that CoQ_{10} attenuates inflammatory reactions.

14. CARDIAC ARREST AND RESUSCITATION

Animal models have demonstrated that CoQ_{10} may play a crucial role during cardiac arrest and prevent reperfusion complications [147, 148].

In one of the studies, 49 patients were randomly assigned either to hypothermia plus CoQ_{10} or hypothermia plus placebo after Cardiopulmonary Resuscitation (CPR). The three-month survival in the CoQ_{10} group was 68% (17 of 25) compared to 29% (7 of 24) in the placebo group (P=0.0413). Nine CoQ_{10} patients versus five placebo patients survived with a Glasgow Outcome Scale of 4 or 5 [149]. Prospective observational study of post-arrest patients demonstrated that CoQ_{10} levels could be named a statistically significant predictor of poor neurologic outcome and in-hospital mortality [150]. These results are similar to other studies, which dem-

onstrated its role in septic and hemorrhagic shocks [151-153]. This underlines the importance of metabolic resuscitation particularly in case of septic shock but may be useful also in other conditions with severely altered hemodynamics [154].

15. FUTURE DIRECTIONS

Several important directions should be prioritized for future CoQ_{10} research. Firstly, the assessment of the optimal dose of CoQ_{10}. High-performance liquid chromatography gives the possibility to establish the plasma concentration, which is optimal for clinical effect. It also allows determining the normal levels of CoQ_{10}, as well as adjusting the dose of administered CoQ_{10}. Secondary, better-powered studies are needed to assess the CoQ_{10} influence on survival in different subgroups of patients. Finally, the introduction of personalized medicine will allow determining who may benefit from supplements.

CONCLUSION

There are many controversial data on the supplementation of CoQ_{10} in different conditions. The reported dosage of CoQ_{10} differs in a wide range 100-300 mg for CV diseases. Limited data on the amount of CoQ_{10} absorbed in the gastrointestinal tract and its amount in the circulating blood were observed. Rat model demonstrates significant impact at a higher dose when the plasma concentration is increased by more than 80%. Future studies should be aimed at assessment of higher dosage of CoQ_{10} administration as well as evaluation of its pharmacokinetics and pharmacodynamics. Overall, there seems to be a beneficial role of CoQ_{10} co-administration as a supplemental therapy in different cardiac and metabolic conditions. The changes in the antioxidant systems in these conditions support the idea that CoQ_{10} may improve outcome, quality of life and decrease morbidity and mortality. Nevertheless, the findings of some studies are based on preclinical or clinical studies with surrogate endpoints. This subject should be addressed in the future. Finally, more randomized trials should be performed to assess the impact of CoQ_{10} supplementation on survival.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Quinzii CM, Lopez LC, Von-Moltke J, *et al*. Respiratory chain dysfunction and oxidative stress correlate with severity of primary CoQ10 deficiency. FASEB J 2008; 22(6): 1874-85.

[2] Sharma A, Fonarow GC, Butler J, Ezekowitz JA, Felker GM. Coenzyme Q10 and heart failure: A state-of-the-art review. Circ Heart Fail 2016; 9(4): e002639.

[3] Deichmann R, Lavie C, Andrews S. Coenzyme Q10 and statin-induced mitochondrial dysfunction. Ochsner J 2010; 10(1): 16-21.

[4] Ayer AMP, Stocker R. CoQ10 function and role in heart failure and ischemic heart disease. Annu Rev Nutr 2015; 2015(35): 175-213.

[5] Mancuso M, Orsucci D, Volpi L, Calsolaro V, Siciliano G. Coenzyme Q10 in neuromuscular and neurodegenerative disorders. Curr Drug Targets 2010; 11(1): 111-21.

[6] Tsai KL, Huang YH, Kao CL, *et al*. A novel mechanism of coenzyme Q10 protects against human endothelial cells from oxidative stress-induced injury by modulating NO-related pathways. J Nutr Biochem 2012; 23(5): 458-68.

[7] Crane FL, Sun IL, Clark MG, Grebing C, Low H. Transplasma-membrane redox systems in growth and development. Biochim Biophys Acta 1985; 811(3): 233-64.

[8] Garrido-Maraver J, Cordero MD, Oropesa-Avila M, *et al*. Coenzyme Q10 therapy. Mol Syndromol 2014; 5(3-4): 187-97.

[9] Alehagen U, Aaseth J, Johansson P. Reduced cardiovascular mortality 10 years after supplementation with selenium and coenzyme Q10 for four years: Follow-up results of a prospective randomized double-blind placebo-controlled trial in elderly citizens. PLoS One 2015; 10(12): e0141641.

[10] Aberg F, Appelkvist EL, Dallner G, Ernster L. Distribution and redox state of ubiquinones in rat and human tissues. Arch Biochem Biophys 1992; 295(2): 230-4.

[11] Miles MV, Horn PS, Morrison JA, Tang PH, DeGrauw T, Pesce AJ. Plasma coenzyme Q10 reference intervals, but not redox status, are affected by gender and race in self-reported healthy adults. Clin Chim Acta 2003; 332(1-2): 123-32.

[12] Singh U, Devaraj S, Jialal I. Coenzyme Q10 supplementation and heart failure. Nutr Rev 2007; 65(6 Pt 1): 286-93.

[13] Kumar A, Kaur H, Devi P, Mohan V. Role of coenzyme Q10 (CoQ10) in cardiac disease, hypertension and Meniere-like syndrome. Pharmacol Ther 2009; 124(3): 259-68.

[14] Bergamini C, Cicoira M, Rossi A, Vassanelli C. Oxidative stress and hyperuricaemia: Pathophysiology, clinical relevance, and therapeutic implications in chronic heart failure. Eur J Heart Fail 2009; 11(5): 444-52.

[15] Lim JY, Park SJ, Hwang HY, *et al*. TGF-beta1 induces cardiac hypertrophic responses *via* PKC-dependent ATF-2 activation. J Mol Cell Cardiol 2005; 39(4): 627-36.

[16] Nakagami H, Takemoto M, Liao JK. NADPH oxidase-derived superoxide anion mediates angiotensin II-induced cardiac hypertrophy. J Mol Cell Cardiol 2003; 35(7): 851-9.

[17] Turunen M, Olsson J, Dallner G. Metabolism and function of coenzyme Q. Biochim Biophys Acta 2004; 1660(1-2): 171-99.

[18] Kayo CY, Carsten ME. Cellular Aspects of Smooth Muscle Function. Pres CU, editor: Cambridge University Press 2005. 209 p.

[19] Yang YK, Wang LP, Chen L, *et al*. Coenzyme Q10 treatment of cardiovascular disorders of ageing including heart failure, hypertension and endothelial dysfunction. Clin Chim Acta 2015; 450: 83-9.

[20] Jung HJ, Park EH, Lim CJ. Evaluation of anti-angiogenic, anti-inflammatory and antinociceptive activity of coenzyme Q(10) in experimental animals. J Pharm Pharmacol 2009; 61(10): 1391-5.

[21] Swarnakar NK, Jain AK, Singh RP, Godugu C, Das M, Jain S. Oral bioavailability, therapeutic efficacy and reactive oxygen species scavenging properties of coenzyme Q10-loaded polymeric nanoparticles. Biomaterials 2011; 32(28): 6860-74.

[22] Kai H, Kuwahara F, Tokuda K, Imaizumi T. Diastolic dysfunction in hypertensive hearts: Roles of perivascular inflammation and reactive myocardial fibrosis. Hypertens Res 2005; 28(6): 483-90.

[23] Bloch MJ. Worldwide prevalence of hypertension exceeds 1.3 billion. J Am Soc Hypertens 2016; 10(10): 753-4.

[24] Hirooka Y, Kishi T, Sakai K, Takeshita A, Sunagawa K. Imbalance of central nitric oxide and reactive oxygen species in the regulation of sympathetic activity and neural mechanisms of hypertension. Am J Physiol Regul Integr Comp Physiol 2011; 300(4): R818-26.

[25] Hirooka Y. Oxidative stress in the cardiovascular center has a pivotal role in the sympathetic activation in hypertension. Hypertens Res 2011; 34(4): 407-12.

[26] Grunfeld S, Hamilton CA, Mesaros S, *et al*. Role of superoxide in the depressed nitric oxide production by the endothelium of genetically hypertensive rats. Hypertension 1995; 26(6 Pt 1): 854-7.

[27] Digiesi V, Cantini F, Oradei A, *et al*. Coenzyme Q10 in essential hypertension. Mol Aspects Med 1994; 15(Suppl): s257-63.

[28] Ignarro LJ. Biological actions and properties of endothelium-derived nitric oxide formed and released from artery and vein. Circ Res 1989; 65(1): 1-21.
[29] Fabre LF, Jr., Banks RC, McIsaac WM, Farrell G. Effects of ubiquinone and related substances on secretion of aldosterone and cortisol. Am J Physiol 1965; 208: 1275-80.
[30] Langsjoen P, Langsjoen P, Willis R, Folkers K. Treatment of essential hypertension with coenzyme Q10. Mol Aspects Med 1994; 15(Suppl): S265-72.
[31] Burke BE, Neuenschwander R, Olson RD. Randomized, double-blind, placebo-controlled trial of coenzyme Q10 in isolated systolic hypertension. South Med J 2001; 94(11): 1112-7.
[32] Ho MJ, Bellusci A, Wright JM. Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension. Cochrane Database Syst Rev 2009; 2009(4): CD007435.
[33] Dai YL, Luk TH, Yiu KH, *et al*. Reversal of mitochondrial dysfunction by coenzyme Q10 supplement improves endothelial function in patients with ischaemic left ventricular systolic dysfunction: a randomized controlled trial. Atherosclerosis 2011; 216(2): 395-401.
[34] Lim SC, Lekshminarayanan R, Goh SK, *et al*. The effect of coenzyme Q10 on microcirculatory endothelial function of subjects with type 2 diabetes mellitus. Atherosclerosis 2008; 196(2): 966-9.
[35] Hamilton SJ, Chew GT, Watts GF. Coenzyme Q10 improves endothelial dysfunction in statin-treated type 2 diabetic patients. Diabetes Care 2009; 32(5): 810-2.
[36] Pedersen HS, Mortensen SA, Rohde M, *et al*. High serum coenzyme Q10, positively correlated with age, selenium and cholesterol, in Inuit of Greenland. A pilot study. Biofactors 1999; 9(2-4): 319-23.
[37] Tiano L, Belardinelli R, Carnevali P, Principi F, Seddaiu G, Littarru GP. Effect of coenzyme Q10 administration on endothelial function and extracellular superoxide dismutase in patients with ischaemic heart disease: A double-blind, randomized controlled study. Eur Heart J 2007; 28(18): 2249-55.
[38] Lee BJ, Tseng YF, Yen CH, Lin PT. Effects of coenzyme Q10 supplementation (300 mg/day) on antioxidation and anti-inflammation in coronary artery disease patients during statins therapy: A randomized, placebo-controlled trial. Nutr J 2013; 12(1): 142.
[39] Buyukkaya E, Evliyaoglu O, Islamoglu Y, *et al*. The relationship between coenzyme Q10 and severity of coronary artery disease. Med Glasnik 2013; 10(2): 229-33.
[40] Lee BJ, Yen CH, Hsu HC, Lin JY, Hsia S, Lin PT. A significant correlation between the plasma levels of coenzyme Q10 and vitamin B-6 and a reduced risk of coronary artery disease. Nutr Res 2012; 32(10): 751-6.
[41] Lee BJ, Lin YC, Huang YC, Ko YW, Hsia S, Lin PT. The relationship between coenzyme Q10, oxidative stress, and antioxidant enzymes activities and coronary artery disease. Sci World J 2012; 2012: 792756.
[42] Lee BJ, Huang YC, Chen SJ, Lin PT. Effects of coenzyme Q10 supplementation on inflammatory markers (high-sensitivity C-reactive protein, interleukin-6, and homocysteine) in patients with coronary artery disease. Nutrition 2012; 28(7-8): 767-72.
[43] Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 385(9963): 117-71.
[44] Mohseni M, Vafa M, Zarrati M, Shidfar F, Hajimiresmail SJ, Rahimi Forushani A. Beneficial effects of coenzyme Q10 supplementation on lipid profile and intereukin-6 and intercellular adhesion molecule-1 reduction, preliminary results of a double-blind trial in acute myocardial infarction. Int J Prevent Med 2015; 6: 73.
[45] Mirhashemi SM, Najafi V, Raygan F, Asemi Z. The effects of coenzyme Q10 supplementation on cardiometabolic markers in overweight type 2 diabetic patients with stable myocardial infarction: A randomized, double-blind, placebo-controlled trial. ARYA Atherosclerosis 2016; 12(4): 158-65.
[46] Mohseni M, Vafa MR, Hajimiresmail SJ, *et al*. Effects of coenzyme Q10 supplementation on serum lipoproteins, plasma fibrinogen, and blood pressure in patients with hyperlipidemia and myocardial infarction. Iran Red Cres Med J 2014; 16(10): e16433.
[47] Sharifi MH, Eftekhari MH, Ostovan MA, Rezaianazadeh A. Effects of a therapeutic lifestyle change diet and supplementation with Q10 plus L-carnitine on quality of life in patients with myocardial infarction: A randomized clinical trial. J Cardiovasc Thoracic Res 2017; 9(1): 21-8.
[48] Serebruany VL, Gurbel PA, Ordonez JV, *et al*. Could coenzyme Q10 affect hemostasis by inhibiting platelet vitronectin (CD51/CD61) receptor? Mol Aspects Med 1997; 18(Suppl): S189-94.
[49] Serebruany VL, Ordonez JV, Herzog WR, *et al*. Dietary coenzyme Q10 supplementation alters platelet size and inhibits human vitronectin (CD51/CD61) receptor expression. J Cardiovasc Pharmacol 1997; 29(1): 16-22.
[50] Serebruany VL, Herzog WR, Atamas SP, *et al*. Hemostatic changes after dietary coenzyme Q10 supplementation in swine. J Cardiovasc Pharmacol 1996; 28(2): 175-81.
[51] Huang CH, Kuo CL, Huang CS, *et al*. High plasma coenzyme Q10 concentration is correlated with good left ventricular performance after primary angioplasty in patients with acute myocardial infarction. Medicine 2016; 95(31): e4501.
[52] Ivanov AV, Gorodetskaya EA, Kalenikova EI, Medvedev OS. Single intravenous injection of coenzyme Q10 protects the myocardium after irreversible ischemia. Bull Exp Biol Med 2013; 155(6): 771-4.
[53] Kalenikova EI, Gorodetskaya EA, Kolokolchikova EG, Shashurin DA, Medvedev OS. Chronic administration of coenzyme Q10 limits postinfarct myocardial remodeling in rats. Biochemistry 2007; 72(3): 332-8.
[54] Lei L, Liu Y. Efficacy of coenzyme Q10 in patients with cardiac failure: A meta-analysis of clinical trials. BMC Cardiovasc Disord 2017; 17(1): 196.
[55] Javed U, Deedwania PC. Beta-adrenergic blockers for chronic heart failure. Cardiol Rev 2009; 17(6): 287-92.
[56] Massie BM, Shah NB. Evolving trends in the epidemiologic factors of heart failure: rationale for preventive strategies and comprehensive disease management. Am Heart J 1997; 133(6): 703-12.
[57] Mahmood SS, Wang TJ. The epidemiology of congestive heart failure: The Framingham Heart Study perspective. Glob Heart 2013; 8(1): 77-82.
[58] Niklowitz P, Sonnenschein A, Janetzky B, Andler W, Menke T. Enrichment of coenzyme Q10 in plasma and blood cells: Defense against oxidative damage. Int J Biol Sci 2007; 3(4): 257-62.
[59] Molyneux SL, Florkowski CM, George PM, *et al*. Coenzyme Q10: an independent predictor of mortality in chronic heart failure. J Am Coll Cardiol 2008; 52(18): 1435-41.
[60] Greenberg S, Frishman WH. Co-enzyme Q10: A new drug for cardiovascular disease. J Clin Pharmacol 1990; 30(7): 596-608.
[61] Mortensen SA, Rosenfeldt F, Kumar A, *et al*. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: A randomized double-blind trial. JACC Heart Fail 2014; 2(6): 641-9.
[62] DiNicolantonio JJ, Bhutani J, McCarty MF, O'Keefe JH. Coenzyme Q10 for the treatment of heart failure: A review of the literature. Open Heart 2015; 2(1): e000326.
[63] Jafari M, Masood Mousavi S, Asgharzadeh A, Yazdani N. Coenzyme Q10 in the treatment of heart failure: A systematic review of systematic reviews. Indian Heart J 2018; in press.
[64] Berman M, Erman A, Ben-Gal T, *et al*. Coenzyme Q10 in patients with end-stage heart failure awaiting cardiac transplantation: A randomized, placebo-controlled study. Clin Cardiol 2004; 27(5): 295-9.
[65] Fotino AD, Thompson-Paul AM, Bazzano LA. Effect of coenzyme Q(1)(0) supplementation on heart failure: A meta-analysis. Am J Clin Nutr 2013; 97(2): 268-75.
[66] Mortensen SA. Overview on coenzyme Q10 as adjunctive therapy in chronic heart failure. Rationale, design and end-points of "Q-symbio"--a multinational trial. BioFactors 2003; 18(1-4): 79-89.
[67] Wang TJ, Larson MG, Levy D, *et al*. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: The Framingham Heart Study. Circulation 2003; 107(23): 2920-5.
[68] Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: Epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003; 91(6A): 2D-8D.
[69] Hynes BJ, Luck JC, Wolbrette DL, *et al*. Atrial fibrillation in patients with heart failure. Curr Opin Cardiol 2003; 18(1): 32-8.
[70] Keith M, Geranmayegan A, Sole MJ, *et al*. Increased oxidative stress in patients with congestive heart failure. J Am Coll Cardiol 1998; 31(6): 1352-6.

[71] Baggio E, Gandini R, Plancher AC, Passeri M, Carmosino G. Italian multicenter study on the safety and efficacy of coenzyme Q10 as adjunctive therapy in heart failure. CoQ10 Drug Surveillance Investigators. Mol Aspects Med 1994; 15(Suppl): s287-94.

[72] Korantzopoulos P, Kolettis TM, Kountouris E. Inflammation and anti-inflammatory interventions in atrial fibrillation. Int J Cardiol 2005; 104(3): 361-2.

[73] Tanaka T, Tsutamoto T, Nishiyama K, *et al*. Impact of oxidative stress on plasma adiponectin in patients with chronic heart failure. Circ J 2008; 72(4): 563-8.

[74] Fazio G, Amoroso GR, Barbaro G, Novo G, Novo S. The role of statins in preventing the progression of congestive heart failure in patients with metabolic syndrome. Curr Pharm Des 2008; 14(25): 2605-12.

[75] Zhao Q, Kebbati AH, Zhang Y, Tang Y, Okello E, Huang C. Effect of coenzyme Q10 on the incidence of atrial fibrillation in patients with heart failure. J Invest Med 2015; 63(5): 735-9.

[76] Kishimoto C, Tamaki S, Matsumori A, Tomioka N, Kawai C. The protection of coenzyme Q10 against experimental viral myocarditis in mice. Jpn Circ J 1984; 48(12): 1358-61.

[77] Kishimoto C, Tomioka N, Nakayama Y, Miyamoto M. Antioxidant effects of coenzyme Q10 on experimental viral myocarditis in mice. J Cardiovasc Pharmacol 2003; 42(5): 588-92.

[78] Shao L, Ma A, Figtree G, Zhang P. Combination therapy with coenzyme Q10 and trimetazidine in patients with acute viral myocarditis. J Cardiovasc Pharmacol 2016; 68(2): 150-4.

[79] Senes M, Erbay AR, Yilmaz FM, *et al*. Coenzyme Q10 and high-sensitivity C-reactive protein in ischemic and idiopathic dilated cardiomyopathy. Clin Chem Lab Med 2008; 46(3): 382-6.

[80] De Blasio MJ, Huynh K, Qin C, *et al*. Therapeutic targeting of oxidative stress with coenzyme Q10 counteracts exaggerated diabetic cardiomyopathy in a mouse model of diabetes with diminished PI3K(p110alpha) signaling. Free Radic Biol Med 2015; 87: 137-47.

[81] Huynh K, Kiriazis H, Du XJ, *et al*. Targeting the upregulation of reactive oxygen species subsequent to hyperglycemia prevents type 1 diabetic cardiomyopathy in mice. Free Radic Biol Med 2013; 60: 307-17.

[82] Manzoli U, Rossi E, Littarru GP, *et al*. Coenzyme Q10 in dilated cardiomyopathy. Int J Tissue React 1990; 12(3): 173-8.

[83] Momomura S, Serizawa T, Ohtani Y, Iizuka M, Sugimoto T. Coenzyme Q10 attenuates the progression of cardiomyopathy in hamsters. Jpn Heart J 1991; 32(1): 101-10.

[84] Soongswang J, Sangtawesin C, Durongpisitkul K, *et al*. The effect of coenzyme Q10 on idiopathic chronic dilated cardiomyopathy in children. Pediatr Cardiol 2005; 26(4): 361-6.

[85] Kocharian A, Shabanian R, Rafiei-Khorgami M, Kiani A, Heidari-Bateni G. Coenzyme Q10 improves diastolic function in children with idiopathic dilated cardiomyopathy. Cardiol Young 2009; 19(5): 501-6.

[86] Langsjoen PH, Langsjoen A, Willis R, Folkers K. Treatment of hypertrophic cardiomyopathy with coenzyme Q10. Mol Aspects Med 1997; 18(Suppl): S145-51.

[87] Adarsh K, Kaur H, Mohan V. Coenzyme Q10 (CoQ10) in isolated diastolic heart failure in hypertrophic cardiomyopathy (HCM). Biofactors 2008; 32(1-4): 145-9.

[88] Conklin KA. Coenzyme q10 for prevention of anthracycline-induced cardiotoxicity. Integr Cancer Ther 2005; 4(2): 110-30.

[89] Greenlee H, Shaw J, Lau YI, Naini A, Maurer M. Lack of effect of coenzyme q10 on doxorubicin cytotoxicity in breast cancer cell cultures. Integr Cancer Ther 2012; 11(3): 243-50.

[90] Mustafa HN, Hegazy GA, Awdan SAE, AbdelBaset M. Protective role of CoQ10 or L-carnitine on the integrity of the myocardium in doxorubicin induced toxicity. Tissue Cell 2017; 49(3): 410-26.

[91] Prince PS, Rajadurai M. Preventive effect of Aegle marmelos leaf extract on isoprenaline-induced myocardial infarction in rats: Biochemical evidence. J Pharm Pharmacol 2005; 57(10): 1353-7.

[92] Sathish V, Ebenezar KK, Devaki T. Synergistic effect of Nicorandil and Amlodipine on tissue defense system during experimental myocardial infarction in rats. Mol Cell Biochem 2003; 243(1-2): 133-8.

[93] Battino M, Ferri E, Gorini A, *et al*. Natural distribution and occurrence of coenzyme Q homologues. Membr Biochem 1990; 9(3): 179-90.

[94] Ghule AE, Kulkarni CP, Bodhankar SL, Pandit VA. Effect of pretreatment with coenzyme Q10 on isoproterenol-induced cardiotoxicity and cardiac hypertrophy in rats. Curr Ther Res Clin Exp 2009; 70(6): 460-71.

[95] Hong H, Zeng JS, Kreulen DL, Kaufman DI, Chen AF. Atorvastatin protects against cerebral infarction via inhibition of NADPH oxidase-derived superoxide in ischemic stroke. Am J Physiol Heart Circ Physiol 2006; 291(5): H2210-5.

[96] Makabe S, Takahashi Y, Watanabe H, Murakami M, Ohba T, Ito H. Fluvastatin protects vascular smooth muscle cells against oxidative stress through the Nrf2-dependent antioxidant pathway. Atherosclerosis 2010; 213(2): 377-84.

[97] Asahi M, Huang Z, Thomas S, *et al*. Protective effects of statins involving both eNOS and tPA in focal cerebral ischemia. J Cereb Blood Flow Metab 2005; 25(6): 722-9.

[98] Folkers K, Langsjoen P, Willis R, *et al*. Lovastatin decreases coenzyme Q levels in humans. Proc Natl Acad Sci USA 1990; 87(22): 8931-4.

[99] Pepe S, Marasco SF, Haas SJ, Sheeran FL, Krum H, Rosenfeldt FL. Coenzyme Q10 in cardiovascular disease. Mitochondrion 2007; 7(Suppl): S154-67.

[100] Manoukian AA, Bhagavan NV, Hayashi T, Nestor TA, Rios C, Scottolini AG. Rhabdomyolysis secondary to lovastatin therapy. Clin Chem 1990; 36(12): 2145-7.

[101] Delbosc S, Morena M, Djouad F, Ledoucen C, Descomps B, Cristol JP. Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are able to reduce superoxide anion production by NADPH oxidase in THP-1-derived monocytes. J Cardiovasc Pharmacol 2002; 40(4): 611-7.

[102] Silva MA, Swanson AC, Gandhi PJ, Tataronis GR. Statin-related adverse events: A meta-analysis. Clin Ther 2006; 28(1): 26-35.

[103] Golomb BA, Evans MA. Statin adverse effects: A review of the literature and evidence for a mitochondrial mechanism. Am J Cardiovasc Drugs 2008; 8(6): 373-418.

[104] Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA 2003; 289(13): 1681-90.

[105] Zita C, Overvad K, Mortensen SA, Sindberg CD, Moesgaard S, Hunter DA. Serum coenzyme Q10 concentrations in healthy men supplemented with 30 mg or 100 mg coenzyme Q10 for two months in a randomised controlled study. Biofactors 2003; 18(1-4): 185-93.

[106] Banach M, Serban C, Sahebkar A, *et al*. Effects of coenzyme Q10 on statin-induced myopathy: A meta-analysis of randomized controlled trials. Mayo Clin Proc 2015; 90(1): 24-34.

[107] Braillon A. Coenzyme Q10 and statin-induced myopathy--II. Mayo Clin Proc 2015; 90(3): 420.

[108] Abd TT, Jacobson TA. Statin-induced myopathy: A review and update. Exp Opin Drug Safety 2011; 10(3): 373-87.

[109] Ghirlanda G, Oradei A, Manto A, *et al*. Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study. J Clin Pharmacol 1993; 33(3): 226-9.

[110] Langsjoen PH, Langsjoen AM. The clinical use of HMG CoA-reductase inhibitors and the associated depletion of coenzyme Q10. A review of animal and human publications. Biofactors 2003; 18(1-4): 101-11.

[111] Silver MA, Langsjoen PH, Szabo S, Patil H, Zelinger A. Statin cardiomyopathy? A potential role for Co-Enzyme Q10 therapy for statin-induced changes in diastolic LV performance: Description of a clinical protocol. Biofactors 2003; 18(1-4): 125-7.

[112] Mortensen SA, Rosenfeldt F, Kumar A, *et al*. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: Results from Q-SYMBIO: A randomized double-blind trial. JACC Heart Fail 2014; 2(6): 641-9.

[113] Silver MA, Langsjoen PH, Szabo S, Patil H, Zelinger A. Effect of atorvastatin on left ventricular diastolic function and ability of coenzyme Q10 to reverse that dysfunction. Am J Cardiol 2004; 94(10): 1306-10.

[114] Stocker R, Pollicino C, Gay CA, *et al*. Neither plasma coenzyme Q10 concentration, nor its decline during pravastatin therapy, is linked to recurrent cardiovascular disease events: A prospective case-control study from the LIPID study. Atherosclerosis 2006; 187(1): 198-204.

[115] Hargreaves IP, Duncan AJ, Heales SJ, Land JM. The effect of HMG-CoA reductase inhibitors on coenzyme Q10: Possible biochemical/clinical implications. Drug Saf 2005; 28(8): 659-76.

[116] Kumar A, Kaur H, Mohan V. Atorvastatin alone/in combination with coenzyme Q10 in 103 cases of ischemic dilated cardiomyopa-

thy. Fourth Conference of the International Coenzyme Q10 Association; LA, USA 2005.

[117] Ates O, Bilen H, Keles S, *et al*. Plasma coenzyme Q10 levels in type 2 diabetic patients with retinopathy. Int J Ophthalmol 2013; 6(5): 675-9.

[118] El-ghoroury EA, Raslan HM, Badawy EA, *et al*. Malondialdehyde and coenzyme Q10 in platelets and serum in type 2 diabetes mellitus: correlation with glycemic control. Blood Coagul Fibrinolysis 2009; 20(4): 248-51.

[119] Sourris KC, Harcourt BE, Tang PH, *et al*. Ubiquinone (coenzyme Q10) prevents renal mitochondrial dysfunction in an experimental model of type 2 diabetes. Free Radic Biol Med 2012; 52(3): 716-23.

[120] Alam MA, Rahman MM. Mitochondrial dysfunction in obesity: Potential benefit and mechanism of Co-enzyme Q10 supplementation in metabolic syndrome. J Diabetes Metab Disord 2014; 13: 60.

[121] Yamashita S, Yamamoto Y. Simultaneous detection of ubiquinol and ubiquinone in human plasma as a marker of oxidative stress. Anal Biochem 1997; 250(1): 66-73.

[122] Hasegawa G, Yamamoto Y, Zhi JG, *et al*. Daily profile of plasma %CoQ10 level, a biomarker of oxidative stress, in patients with diabetes manifesting postprandial hyperglycaemia. Acta Diabetol 2005; 42(4): 179-81.

[123] Shen Q, Pierce JD. Supplementation of coenzyme Q10 among patients with type 2 diabetes mellitus. Healthcare 2015; 3(2): 296-309.

[124] Gall M-A, Borch-Johnsen K, Hougaard P, Nielsen FS, Parving H-H. Albuminuria and poor glycemic control predict mortality in NIDDM. Diabetes 1995; 44(11): 1303-9.

[125] Suksomboon N, Poolsup N, Juanak N. Effects of coenzyme Q10 supplementation on metabolic profile in diabetes: A systematic review and meta-analysis. J Clin Pharm Therapeut 2015; 40(4): 413-8.

[126] Raygan F, Rezavandi Z, Dadkhah Tehrani S, Farrokhian A, Asemi Z. The effects of coenzyme Q10 administration on glucose homeostasis parameters, lipid profiles, biomarkers of inflammation and oxidative stress in patients with metabolic syndrome. Eur J Nutr 2016; 55(8): 2357-64.

[127] Samimi M, Zarezade Mehrizi M, Foroozanfard F, *et al*. The effects of coenzyme Q10 supplementation on glucose metabolism and lipid profiles in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. Clin Endocrinol 2017; 86(4): 560-6.

[128] Maheshwari RA, Balaraman R, Sen AK, Seth AK. Effect of coenzyme Q10 alone and its combination with metformin on streptozotocin-nicotinamide-induced diabetic nephropathy in rats. Indian J Pharmacol 2014; 46(6): 627-32.

[129] Maheshwari R, Balaraman R, Sen AK, Shukla D, Seth A. Effect of concomitant administration of coenzyme Q10 with sitagliptin on experimentally induced diabetic nephropathy in rats. Ren Fail 2017; 39(1): 130-9.

[130] Littarru GP, Tiano L. Clinical aspects of coenzyme Q10: An update. Nutrition 2010; 26(3): 250-4.

[131] Quiles JL, Ochoa JJ, Battino M, *et al*. Life-long supplementation with a low dosage of coenzyme Q10 in the rat: effects on antioxidant status and DNA damage. Biofactors 2005; 25(1-4): 73-86.

[132] Lee SK, Lee JO, Kim JH, *et al*. Coenzyme Q10 increases the fatty acid oxidation through AMPK-mediated PPARalpha induction in 3T3-L1 preadipocytes. Cell Signal 2012; 24(12): 2329-36.

[133] Mohr D, Stocker R. Radical-mediated oxidation of isolated human very-low-density lipoprotein. Arterioscler Thromb 1994; 14(7): 1186-92.

[134] Pechan I, Olejarova I, Danova K, *et al*. Antioxidant status of patients after on-pump and off-pump coronary artery bypass grafting. Bratislavske Lekarske Listy 2004; 105(2): 45-50.

[135] Rosenfeldt F, Marasco S, Lyon W, *et al*. Coenzyme Q10 therapy before cardiac surgery improves mitochondrial function and *in vitro* contractility of myocardial tissue. J Thorac Cardiovasc Surg 2005; 129(1): 25-32.

[136] Hocum Stone L, Butterick TA, Duffy C, *et al*. Cardiac strain in a swine model of regional hibernating myocardium: Effects of CoQ10 on contractile reserve following bypass surgery. J Cardiovasc Transl Res 2016; 9(4): 368-73.

[137] Leong JY, van der Merwe J, Pepe S, *et al*. Perioperative metabolic therapy improves redox status and outcomes in cardiac surgery patients: a randomised trial. Heart Lung Circ 2010; 19(10): 584-91.

[138] Hadj A, Esmore D, Rowland M, *et al*. Pre-operative preparation for cardiac surgery utilising a combination of metabolic, physical and mental therapy. Heart Lung Circ 2006; 15(3): 172-81.

[139] Makhija N, Sendasgupta C, Kiran U, *et al*. The role of oral coenzyme Q10 in patients undergoing coronary artery bypass graft surgery. J Cardiothorac Vasc Anesthesia 2008; 22(6): 832-9.

[140] Chello M, Mastroroberto P, Romano R, *et al*. Protection by coenzyme Q10 from myocardial reperfusion injury during coronary artery bypass grafting. Ann Thorac Surg 1994; 58(5): 1427-32.

[141] Tanaka J, Tominaga R, Yoshitoshi M, *et al*. Coenzyme Q10: The prophylactic effect on low cardiac output following cardiac valve replacement. Ann Thorac Surg 1982; 33(2): 145-51.

[142] Taggart DP, Jenkins M, Hooper J, *et al*. Effects of short-term supplementation with coenzyme Q10 on myocardial protection during cardiac operations. Ann Thorac Surg 1996; 61(3): 829-33.

[143] Gvozdjakova A, Kucharska J, Mizera S, *et al*. Coenzyme Q10 depletion and mitochondrial energy disturbances in rejection development in patients after heart transplantation. Biofactors 1999; 9(2-4): 301-6.

[144] Kucharska J, Gvozdjakova A, Mizera S, *et al*. Participation of coenzyme Q10 in the rejection development of the transplanted heart: A clinical study. Physiol Res 1998; 47(6): 399-404.

[145] Tomasetti M, Alleva R, Piva R, *et al*. Evaluation of ischemia-reperfusion damage during coronary angioplasty. Electrocardiographic assessment and biochemical modifications in blood from the coronary sinus. Italian Heart J 2000; 1(3): 216-20.

[146] Aslanabadi N, Safaie N, Asgharzadeh Y, *et al*. The randomized clinical trial of coenzyme Q10 for the prevention of periprocedural myocardial injury following elective percutaneous coronary intervention. Cardiovasc Therap 2016; 34(4): 254-60.

[147] Ren Z, Ding W, Su Z, *et al*. Mechanisms of brain injury with deep hypothermic circulatory arrest and protective effects of coenzyme Q10. J Thorac Cardiovasc Surg 1994; 108(1): 126-33.

[148] Mori F, Mohri H. Effects of coenzyme Q10 added to a potassium cardioplegic solution for myocardial protection during ischemic cardiac arrest. Ann Thorac Surg 1985; 39(1): 30-6.

[149] Damian MS, Ellenberg D, Gildemeister R, *et al*. Coenzyme Q10 combined with mild hypothermia after cardiac arrest: A preliminary study. Circulation 2004; 110(19): 3011-6.

[150] Cocchi MN, Giberson B, Berg K, *et al*. Coenzyme Q10 levels are low and associated with increased mortality in post-cardiac arrest patients. Resuscitation 2012; 83(8): 991-5.

[151] Donnino MW, Mortensen SJ, Andersen LW, *et al*. Ubiquinol (reduced Coenzyme Q10) in patients with severe sepsis or septic shock: A randomized, double-blind, placebo-controlled, pilot trial. Crit Care 2015; 19: 275.

[152] Donnino MW, Cocchi MN, Salciccioli JD, *et al*. Coenzyme Q10 levels are low and may be associated with the inflammatory cascade in septic shock. Crit Care 2011; 15(4): R189.

[153] Shen Q, Holloway N, Thimmesch A, Wood JG, Clancy RL, Pierce JD. Ubiquinol decreases hemorrhagic shock/resuscitation-induced microvascular inflammation in rat mesenteric microcirculation. Physiol Rep 2014; 2(11): 1.

[154] Leite HP, de Lima LF. Metabolic resuscitation in sepsis: a necessary step beyond the hemodynamic? J Thorac Dis 2016; 8(7): E552-7.