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

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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 Q10 (CoQ10) is an essential compound of the human body. There is growing evidence that CoQ10 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 CoQ10 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 Q10, 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 Q10 (CoQ10) is an essential compound of the human body which is synthesized in the mitochondrial inner membrane [1]. The molecule of CoQ10 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 CoQ10 exists in 2 forms: oxidized (ubiquinone) and reduced (ubiquinol) [1].

CoQ10 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]. CoQ10 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 CoQ10, 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). CoQ10 formula.

In addition to its important role in electrons’ transport, CoQ10 can act as an intercellular antioxidant, protecting the plasmatic membrane against peroxidation [5]. In a research, supplementation with CoQ10 showed an obvious decrease of the lipid hydroperoxides’ concentration in atherosclerotic lesions in apolipoprotein E-deficient mice [6]. As a hydrogen...
donor, it is more effective than other antioxidants. Besides that CoQ₁₀ 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 ubiquinone 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 CoQ₁₀’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 CoQ₁₀ in a variety of cardiovascular and metabolic conditions with an analysis of its impact on patients’ health and quality of life.

2. FUNCTIONS OF COQ₁₀ IN HEART DISEASES

In the body, CoQ₁₀ 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 CoQ₁₀. It was noticed that CoQ₁₀’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 CoQ₁₀ decreases in direct proportion to disease progression [13]. There are several theories about the role of CoQ₁₀’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 CoQ₁₀ stops the initial process of lipid peroxyl radicals’ formation. That is the reason why CoQ₁₀ is considered to be a very potent antioxidant against ROS and free radicals in biological membranes [17].

Secondly, CoQ₁₀ plays a great role in the heart’s energetic needs. For example, the process of cardiac contraction, which involves the release of Ca²⁺ 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, CoQ₁₀ is the main component in the transport of electrons necessary for ATP production.

| Organ      | Ubiquinone Concentration (µg/g) | Ubiquinol Concentration (µg/g) | Effects                        | References       |
|------------|---------------------------------|--------------------------------|--------------------------------|------------------|
| Heart      | 132.0                           | 61.0                           | Antioxidant                    |                  |
| Kidneys    | 77.0                            | 75.0                           | Bioenergetic                   |                  |
| Liver      | 63.6                            | 95.0                           | Anti-inflammatory              |                  |
| Muscle     | 39.7                            | 65.0                           | Membrane stabilizer            |                  |
| Brain      | 13.4                            | 23.0                           | Antiatherogenic                |                  |
| Pancreas   | 32.7                            |                                 |                                | Aberg et al. [10]|
| Spleen     | 24.6                            |                                 |                                | Miles et al. [11]|
| 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                           |                                |                  |
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 CoQ10 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 CoQ10 administration in different conditions are presented in Table 2.

3. CoQ10 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 oxide activate hypertension’s 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. CoQ10 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 CoQ10 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 CoQ10 adjusts the angiotensin effect in sodium retention and decreases the level of aldosterone [29]. This effect was proved in a study where CoQ10 was administrated as an adjuvant to usual antihypertensive therapy to keep serum level of CoQ10 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 CoQ10 administration, the systolic blood pressure was lowered to normal limits [31]. In another systematic review [32], it was assumed that CoQ10 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 CoQ10 didn’t modify the blood pressure [33-35]. In other words, the antihypertensive effect of CoQ10 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 CoQ10. For example, it was noticed that in Indian males, the plasma level of CoQ10 is considerably lower than

| Condition                  | Possible Effects                                                                 | References |
|----------------------------|---------------------------------------------------------------------------------|------------|
| Hypertension               | Scavenging of ROS                                                             | [27-29]    |
|                            | Vaso dilatation                                                                |            |
|                            | Angiotensin effect adjustment                                                  |            |
|                            | Aldosterone level reducing                                                    |            |
| T2DM                       | Protection against ROS                                                         | [130-132]  |
|                            | Antioxidant                                                                    |            |
|                            | Fatty acid oxidation enhancement                                               |            |
| Metabolic syndrome         | Protection against ROS                                                         | [115, 133] |
|                            | Antioxidant                                                                    |            |
|                            | Tissue-protective                                                              |            |
|                            | The increase in triglyceride-rich lipoproteins (VLDL)                          |            |
| Overall role in cardiovascular disease | Antioxidant                                                               | [14, 18, 19] |
|                            | Protection against ROS                                                         |            |
|                            | Bioenergetic                                                                   |            |
|                            | Anti-inflammatory                                                             |            |
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 administered 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 fibronectin-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 CoQ10 improves the oxygen utilization on the cellular level.

In a randomized controlled multicenter trial that evaluated patients with HF that received 100 mg CoQ10 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 CoQ10 group after 2 years (p=0.028) [61]. Another Q-Symbio trial demonstrated the inter-influence between CoQ10 and HF endpoints during 2 years CoQ10/placebo administration. CoQ10 remarkably diminished the long-term endpoint (cardiovascular morbidity) in the group which administered placebo (the adverse effect was noticed just in 15% patients vs. 26%, p=0.003) [62]. Generally, Q-Symbio studies showed that CoQ10 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 CoQ10 and placebo were almost the same.

The administration of CoQ10 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 CoQ10 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 CoQ10 refill [66].

7. CoQ10 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].

CoQ10 plays an important role in oxidative phosphorylation, 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 CoQ10 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 CoQ10 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 CoQ10 group. Three patients (6.3%) in the CoQ10 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 CoQ10 than in the control group [76]. Histologic examination showed that the severity of myocarditis was less in the CoQ10 group. The inflammatory process induced by the virus was suppressed by the CoQ10 treatment. Thus, pre-treatment with CoQ10 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 CoQ10 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 CoQ10 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].

CoQ10 deficiency is frequently encountered in dilated cardiomyopathy and this may be reversible by the CoQ10 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, CoQ10 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 CoQ10. All patients noted improvement in symptoms of fatigue and dyspnea without any 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. **CoQ10 AND CARDIOTOXICITY**

The latest studies hypothesize the role of CoQ10 in cardiotoxicity, induced by some drugs.

One of the groups of drugs used in chemotherapy is an 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 CoQ10 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 CoQ10 did not have any influence on doxorubicin cell toxicity thus there is a need for further studies [89].

Later, it was found, that CoQ10 and L-carnitine administration, started within 5 days before doxorubicin use, improved heart’s functions, decreased Troponin-I, 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 CoQ10 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]. CoQ10 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. **CoQ10 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 CoQ10 is similar (mevalonate pathway). Therefore, HMG-CoA reductase inhibitors block cholesterol synthesis and CoQ10 ones by reducing the level of farnesyl pyrophosphate [98]. The depletion of CoQ10 is really important in elderly because with time, the endogenous level of CoQ10 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. CoQ10 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 CoQ10, 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 CoQ10 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 CoQ10 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 CoQ10 [116].

12. **CoQ10 TYPE 2 DIABETES AND METABOLIC SYNDROME**

It is often observed that there is CoQ10 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 CoQ10. Thus leading to the idea that it can also influence the glycemia levels [120].

As it was mentioned before, there are two forms of CoQ10: 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 co-workers, who considered that CoQ10 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 CoQ₁₀ 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 CoQ₁₀ 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, CoQ₁₀ 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 CoQ₁₀ 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 CoQ₁₀ 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 CoQ₁₀ showed a better renoprotective effect than CoQ₁₀ or metformin alone [128]. This is also true for other drugs such as sitagliptin [129]. This brings up an important point that CoQ₁₀ 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 CoQ₁₀ 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 CoQ₁₀ exhibited a greater recovery of developed force compared with those in patients receiving placebo. This leads to the conclusion that preoperative oral CoQ₁₀ therapy in patients undergoing cardiac surgery increases myocardial and cardiac mitochondrial CoQ₁₀ 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 CoQ₁₀ administration of 10 mg/kg/day were evaluated with MRI at 4-week following Coronary Artery Bypass Graft Surgery (CABG). CoQ₁₀ 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 (CoQ₁₀, 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 CoQ₁₀. Similar studies advocate for a more complex management of the patients, which should include metabolic (CoQ₁₀, 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 post-operative recovery [138].

There are also reports that patients who received CoQ₁₀ 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 CoQ₁₀ 12 hours before the procedure [142].

Furthermore, the CoQ₁₀ level may play a role in heart rejection after a transplant. CoQ₁₀ level and mitochondrial bioenergetic functions of endomyocardial biopsies contribute to the explanation of pathobioc hemical mechanisms of rejection thus CoQ₁₀ therapy could contribute to the prevention of rejection of the transplanted heart [143]. Myocardial and blood CoQ₁₀ 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 CoQ₁₀ 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 CoQ₁₀ 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 CoQ₁₀ group [146]. This supports the evidence that CoQ₁₀ attenuates inflammatory reactions.

14. CARDIAC ARREST AND RESUSCITATION

Animal models have demonstrated that CoQ₁₀ 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 CoQ₁₀ or hypothermia plus placebo after Cardiopulmonary Resuscitation (CPR). The three-month survival in the CoQ₁₀ group was 68% (17 of 25) compared to 29% (7 of 24) in the placebo group (P=0.0413). Nine CoQ₁₀ 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 CoQ₁₀ 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 CoQ10 research. Firstly, the assessment of the optimal dose of CoQ10. 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 CoQ10, as well as adjusting the dose of administered CoQ10. Secondary, better-powered studies are needed to assess the CoQ10 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 CoQ10 in different conditions. The reported dosage of CoQ10 differs in a wide range 100-300 mg for CV diseases. Limited data on the amount of CoQ10 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 CoQ10 administration as well as evaluation of its pharmacokinetics and pharmacodynamics. Overall, there seems to be a beneficial role of CoQ10 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 CoQ10 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 CoQ10 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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