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Review Article

Cardiovascular Effects of Coenzyme Q10

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ABSTRACT

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

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

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

BACKGROUND

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

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

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

ATHEROSCLEROSIS

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

The immune system and inflammatory response play a decisive role in initiation and progression of atherosclerotic changes, that the condition could be classified into inflammatory diseases

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[12,13]. Besides, the mitochondrial dysfunction could result in the progression of disease, as it increases ROS activities, and oxidative stress damages [14]. CoQ10 prescription could be a promising alternative treatment for atherosclerosis, as it could regulate inflammation, mitochondrial energy, gene expression, oxidative state of cell membranes [6,15-17].

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

HYPERTENSION

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

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

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

CORONARY ARTERY DISEASE

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

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

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

MYOCARDIAL INFARCTION

Myocardial infarction (MI) is a medical condition that can lead to considerable rates of morbidity and mortality. MI could be among the first manifestations of CAD, or it might happen, recurrently, in cases with the diagnosed disease [40].

It is believed that the prescription of CoQ10 could be beneficial in patient with MI, and the underlying mechanisms are assumed to be the improvement of mitochondrial dysfunction and mitigation of DNA damage by anti-oxidative effect of the agent [41].

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

CONGESTIVE HEART FAILURE

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

CoQ10 supplementation could ameliorate cardiac output, which means that they can enhance cardiac contractility [53]. The subjective data, and the symptoms of heart failure such as cyanosis, rales, dyspnea, palpitation, jugular reflux, hepatomegaly,

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

CARDIOMYOPATHY

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

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

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

METABOLIC SYNDROME

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

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

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

ARRHYTHMIAS

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

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

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

CARDIAC SURGERY

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

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

Clinical trials showed beneficial effects of CoQ10 in the setting of cardiothoracic surgery [26]. Administration of CoQ10 prior to cardiac surgery for 2 weeks resulted in better post-operative status, improved contractile function, and increased mitochondrial energy production, besides it also increased myocardial tolerance to *in vitro* hypoxia-re-oxygenation stress [53]. In a randomized double-blind clinical trial, patients who underwent CABG or valve surgery and received CoQ10 (100 mg 3 times a day) for at least two weeks had lower myocardial damage, enhanced redox state, and decreased duration of postoperative hospitalization [84]. However, an investigation showed that four weeks treatment with CoQ10 in the animal models that underwent CABG did not enhance the contractile reserve, and also did not reduce oxidative stress in the mitochondria (Table 1) [85].

Table 1: Cardiovascular effects of CoQ10.

Condition	Biological mechanisms	Functional effects	Human studies approving the effect and related dosage of drug
Atherosclerosis	Anti-inflammatory	Suppressive effect on pro-inflammatory substances such as nuclear factor κB (NFκB)	A controlled, double-blind trial by Zeb et al.: 120 mg/day for 1 year
	Bio-energetic		
	Gene expression		
	Antioxidant		
Hypertension	Scavenging of ROS	Reducing peripheral vascular resistant	A meta-analysis: by Rosenfeldt et al. : 34 mg/day to 225 mg/day in trial, 75 mg to 360 mg in studies
	Antioxidant	Angiotensin effect adjustment	
	Increasing endothelial NO	Aldosterone level reducing	
Coronary artery disease	Antioxidant	Increasing post-ischemic recovery	A randomized, double-blind, controlled trial by Singh et al.: 120 mg/day for 28 days
		Lowering blood viscosity in patients with ischemic heart disease	
		Increasing treadmill exercise tolerance with less ST-segment depression	A randomized, double-blind, controlled trial by Singh et al.: 120 mg/day for 1 year
	Anti-inflammatory	Reduction in angina and reduction in nitroglycerin use was noted in patients with stable	
		Improvement of anginal pain scores, left ventricular dysfunction, and arrhythmia	A randomized placebo-controlled trial by Lee et al.: 300 mg/day for 12 weeks
Myocardial infarction	Improving mitochondrial dysfunction	Less severity of degeneration and necrosis	An observational study by Huang et al.: 6 month follow-up considering Plasma CoQ10 concentration
		Higher levels of H unit of LDL	
	Antioxidant	Accelerated recovery	A randomized, double-blind, placebo-controlled trial by Mirhashemi et al.: 100 mg/day for 8 weeks
		Reduction of angina, arrhythmia, and left ventricular dysfunction	
Congestive heart failure	Improving mitochondrial dysfunction	Elevation of stroke volume	A double-blind, randomized trial by Mortensen et al.: 300 mg/day for 2 years
	Improving endothelial dysfunction	Elevation of EF	
	Anti-inflammatory	Enhancing cardiac output	
	Maintaining myocardium	Enhancing cardiac index	A meta-analysis by Lei et al.: not uniformed dosage and duration
		Enhancing diastolic volume index	
Cardiomyopathy	Antioxidant	Reduce fibrosis	A controlled-placebo prospective study by Kumar et al.: 200 mg/day with 9.4 months to 27.5 months of follow-up
		Enhance left ventricular dysfunction	
		Reduce cardiomyocyte hypertrophy	
	Anti-inflammatory	Elevating of EF	A double-blind, placebo-controlled prospective trial by Kocharian et al.: 2 mg/kg/day for six months(pediatrics)
		Preventing drug-induced cardiomyopathy	
Metabolic syndrome	Antioxidant	Increasing very low density lipoprotein (VLDL)	A randomized trial by Raygan et al.: 100 mg/day for 8 weeks
	Tissue-protection	Elevating serum insulin	
	Protection against ROS	Lowering blood pressure	
	improving endothelial dysfunction		
Arrhythmia	Bio-energetic	Preventing QT_interval prolongation	A randomized controlled clinical trial by Zhao et al.: 30 mg/day for 12 months
	Lowering the level of malodialdehyde		
	Anti-inflammatory	Reduction in ventricular premature beats	
	Antioxidant		
Cardiac surgery	Anti-inflammatory	Increasing myocardial tolerance to hypoxia-re-oxygenation stress	A randomized double-blind clinical trial by Leong et al.: 300 mg/day before and one month after surgery for at least two weeks
	Antioxidant		
	Bio-energetic	Improving contractile function	
	Scavenging of ROS		
SAMS	Improving mitochondrial dysfunction	Reverse statin-induced myopathy	A small pilot study by Caso et al.:100 mg/day for 30 days
	Bio-energetic	Mild-to moderate reduction of muscular symptoms of statin-therapy	A randomized clinical study by Skarlovnik et al.: 100 mg/day for 30 days

Note: ROS: Reactive Oxygen Species; NO: Nitric Oxide; LDL: Low-Density Lipoproteins; EF: Ejection Fraction; VLDL: Very Low Density Lipoprotein

COQ10 AND HMG-COA REDUCTASES

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

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

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

CONCLUSION

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

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REFERENCES

1. Crane FL, Hatefi Y, Lester RL, Widmer C. Isolation of a quinone from beef heart mitochondria. Biochim Biophys Acta. 1957; 25:220-221.
2. Jafari M, Mousavi SM, Asgharzadeh A, Yazdani N. Coenzyme Q10 in the treatment of heart failure: A systematic review of systematic reviews. Indian Heart J. 2018; 70:S111-S117.
3. Raizner AE. Coenzyme Q10. Methodist Debakey Cardiovasc J. 2019; 15(3):185.
4. Carmona MC, Lefebvre P, Lefebvre B, Galinier A, Benani A, Jeanson Y, et al. Coadministration of coenzyme Q prevents rosiglitazone-induced adipogenesis in ob/ob mice. Int J Obes. 2009; 33(2):204-211.
5. Arroyo A, Kagan VE, Tyurin VA, Burgess JR, de Cabo R, Navas P, et al. NADH and NADPH-dependent reduction of coenzyme Q at the plasma membrane. Antioxid Redox Signal. 2000; 2(2):251-262.
6. Barbara Sarter P. Coenzyme Q10 and cardiovascular disease: A review. J Cardiovasc Nurs. 2002; 16(4):9-20.
7. 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):259-268.
8. Molyneux SL, Florkowski CM, George PM, Pilbrow AP, Frampton CM, Lever M, et al. Coenzyme Q10: an independent predictor of mortality in chronic heart failure. Am Coll Cardiol. 2008; 52:1435-1441.
9. Kontush A, Reich A, Baum K, Spranger T, Finckh B, Kohlschütter A, et al. Plasma ubiquinol-10 is decreased in patients with hyperlipidemia. Atherosclerosis. 1997; 129(1):119-126.
10. Lusis AJ. Atherosclerosis. Nature. 2000; 407(6801):233-41.
11. Thomas H, Diamond J, Vieco A, Chaudhuri S, Shinnar E, Cromer S, et al. Global atlas of cardiovascular disease. Global heart. 2018;13(3).
12. Wu MY, Li CJ, Hou MF, Chu PY. New insights into the role of inflammation in the pathogenesis of atherosclerosis. Int J Mol Sci. 2017; 18(10):2034.
13. Fredman G, Tabas I. Boosting inflammation resolution in atherosclerosis: The next frontier for therapy. Am J Pathol. 2017; 187(6):1211-1221.
14. Peng W, Cai G, Xia Y, Chen J, Wu P, Wang Z, et al. Mitochondrial dysfunction in atherosclerosis. DNA Cell Biol. 2019; 38(7):597-606.
15. Doring F, Schmelzer C, Lindner I, Vock C, Fujii K. Functional connections and pathways of coenzyme Q10-inducible genes: An in-silico study. IUBMB Life. 2007; 59(10):628-633.
16. Bentinger M, Tekle M, Dallner G. Coenzyme Q-Biosynthesis and functions. Biochem Biophys Res Commun. 2010; 396(1):74-79.
17. Schmidt AJ, Heiser P, Hemmeter UM, Krieg J-C, Vedder H. Effects of antidepressants on mRNA levels of antioxidant enzymes in human monocytic U-937 cells. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32(6): 1567-1573.
18. Littarru GP, Tiano L. Bioenergetic and antioxidant properties of coenzyme Q10: Recent developments. Mol Biotechnol. 2007; 37(1):31-37.
19. Xie T, Wang C, Jin Y, Meng Q, Liu Q, Wu J, et al. CoenzymeQ10-induced activation of AMPK-YAP-OPA1 pathway alleviates atherosclerosis by improving mitochondrial function, inhibiting oxidative stress and promoting energy metabolism. Front Pharmacol. 2020; 11:1034.

20. Zeb I, Ahmadi N, Kadakia J, Larijani VN, Flores F, Li D, et al. Aged garlic extract and coenzyme Q10 have favorable effect on inflammatory markers and coronary atherosclerosis progression: A randomized clinical trial. J Cardiovasc Dis Res. 2012; 3(3):185-190.

21. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020; 16(4):223-237.

22. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global disparities of hypertension prevalence and control: A systematic analysis of population-based studies from 90 countries. Circulation. 2016; 134(6):441-450.

23. 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-R826.

24. Sood B, Keenaghan M. Coenzyme Q10. StatPearls [Internet]: StatPearls Publishing; 2020.

25. Grunfeld S, Hamilton CA, Mesaros S, McClain SW, Dominiczak AF, Bohr DF, et al. Role of superoxide in the depressed nitric oxide production by the endothelium of genetically hypertensive rats. Hypertension. 1995; 26(6):854-857.

26. Pepe S, Marasco SF, Haas SJ, Sheeran FL, Krum H, Rosenfeldt FL. Coenzyme Q10 in cardiovascular disease. Mitochondrion. 2007; 7(1):S154-S67.

27. Gao L, Mao Q, Cao J, Wang Y, Zhou X, Fan L. Effects of coenzyme Q10 on vascular endothelial function in humans: A meta-analysis of randomized controlled trials. Atherosclerosis. 2012; 221(2):311-316.

28. Rosenfeldt FL, Haas SJ, Krum H, Hadj A, Ng K, Leong JY, et al. Coenzyme Q10 in the treatment of hypertension: A meta-analysis of the clinical trials. J Human Hypertens. 2007; 21(4):297-306.

29. Young JM, Florkowski CM, Molyneux SL, McEwan RG, Frampton CM, Nicholls MG, et al. A randomized, double-blind, placebo-controlled crossover study of coenzyme Q10 therapy in hypertensive patients with the metabolic syndrome. Am J Hypertens. 2012; 25(2):261-270.

30. Mastoi Q, Wah TY, Gopal Raj R, Iqbal U. Automated diagnosis of coronary artery disease: A review and workflow. Cardiol Res Pract. 2018; 2018:1-9.

31. Cardiovascular Diseases. 2020.

32. Siegel D, Devaraj S, Mitra A, Raychaudhuri SP, Raychaudhuri SK, Jialal I. Inflammation, atherosclerosis, and psoriasis. Clin Rev Allergy Immunol. 2013; 44(2):194-204.

33. Singh U, Devaraj S, Jialal I. Coenzyme Q10 supplementation and heart failure. Nutr Rev. 2008; 65(6):286-293.

34. 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; 2012:1-8.

35. Rosenfeldt F, Pepe S, Linnane A, Nagley P, Rowland M, Ou R, et al. Coenzyme Q10 protects the aging heart against stress: Studies in rats, human tissues and patients. Ann NY Acad Sci. 2002; 959(1):355-359.

36. Singh RB, Wander GS, Rastogi A, Shukla PK, Mittal A, Sharma JP, et al. Randomized, double-blind placebo controlled trial of coenzyme Q10 in patients with acute myocardial infarction. Cardiovasc Drugs Ther. 1998; 12(4):347-353.

37. Singh RB, Neki NS, Kartikey K, Pella D, Kumar A, Niaz MA, et al. Effect of coenzyme Q10 on risk of atherosclerosis in patients with recent myocardial infarction. Biochem. 2003; 246(1-2):75-82.

38. Kumar A, Kaur H, Mohan V. Adjunctive coenzyme q10 therapy in 106 cases of Acute Coronary Syndrome (ACS). In: Fourth Conference of the International Coenzyme Q10 Association. 2005.

39. 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.

40. Alpert JS. The fourth edition of the universal definition of myocardial infarction. Am J Med. 2018; 131(11):1265-1266.

41. Huang CH, Kuo CL, Huang CS, Tseng WM, Lian IB, Chang CC, 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.

42. Eleawa SM, Alkhateeb M, Ghosh S, Al-Hashem F, Shatoor AS, Alhejaily A, et al. Coenzyme Q10 protects against acute consequences of experimental myocardial infarction in rats. Int J Physiol Pathophysiol Pharmacol. 2015; 7(1):1-13.

43. 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):771-774.

44. 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 Atheroscler. 2016; 12(4):158.

45. Gumieniczek A, Hopkała H, Roliński J, Bojarska-Junak A. Interleukin-6 and oxidative stress in plasma of alloxan-induced diabetic rabbits after pioglitazone treatment. Immunopharmacol Immunotoxicol. 2006; 28(1):81-91.

46. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American college of cardiology foundation/American heart association task force on practice guidelines. J Am Coll Cardiol. 2013; 62(16):e147-e239.

47. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, 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):2920-2925.

48. Ruddox V, Sandven I, Munkhaugen J, Skattebu J, Edvardsen T, Otterstad JE. Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: A systematic review and meta-analysis. Eur J Prev Cardiol. 2017; 24(14):1555-1566.

49. Littarru GP. Location and function of coenzyme Q in the respiratory chain. In: Energy and defense. Facts and perspectives on coenzyme Q10 in biology and medicine. Casa Editrice Scientifica Internazionale, Rome. 1994:14-22.

50. Opie LH. The metabolic vicious cycle in heart failure. Lancet. 2004; 364(9447):1733-1734.

51. Belardinelli R, Muçaj A, Lacalaprice F, Solenghi M, Seddaiu G, Principi F, et al. Coenzyme Q10 and exercise training in chronic heart failure. Eur Heart J. 2006; 27(22):2675-2681.

52. Rosenfeldt F, Marasco S, Lyon W, Wowk M, Sheeran F, Bailey M, 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.

53. Greenberg S, Frishman WH. Co-enzyme Q10: A new drug for cardiovascular disease. J Clin Pharmacol. 1990; 30(7):596-608.

54. Soja AM, Mortensen SA. Treatment of congestive heart failure with coenzyme Q10 illuminated by meta-analyses of clinical trials. Mol Aspects Med. 1997; 18:159-168.

55. Sander S, Coleman CI, Patel AA, Kluger J, White CM. The impact of coenzyme Q10 on systolic function in patients with chronic heart failure. J Card Fail. 2006; 12:464-472.

56. Mortensen SA, Rosenfeldt F, Kumar A, Dolliner P, Filipiak KJ, Pella D, et al. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: A randomized double-blind trial. J Am Coll Cardiol Heart Fail. 2014; 2(6):641-649.

57. 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):1-7.

58. Schultheiss HP, Fairweather D, Caforio AL, Escher F, Hershberger RE, Lipshultz SE, et al. Dilated cardiomyopathy. Nat Rev Dis Primers. 2019; 5(1):1-19.

59. McKenna WJ, Maron BJ, Thiene G. Classification, epidemiology, and global burden of cardiomyopathies. Circ Res. 2017; 121(7):722-730.

60. Braunwald E. Cardiomyopathies: An overview. Circ Res. 2017; 121(7):711-721.

61. Şeneş M, Erbay AR, Yılmaz FM, Topkaya BÇ, Zengi O, Doğan M, et al. Coenzyme Q10 and high-sensitivity C-reactive protein in ischemic and idiopathic dilated cardiomyopathy. Clin Chem Lab Med. 2008; 46(3):382-386.

62. De Blasio MJ, Huynh K, Qin C, Rosli S, Kiriazis H, Ayer A, et al. Therapeutic targeting of oxidative stress with coenzyme Q10 counteracts exaggerated diabetic cardiomyopathy in a mouse model of diabetes with diminished PI3K (p110α) signaling. Free Radic Biol Med. 2015; 87:137-147.

63. Huynh K, Kiriazis H, Du X-J, Love JE, Gray SP, Jandeleit-Dahm KA, et al. Targeting the upregulation of reactive oxygen species subsequent to hyperglycemia prevents type 1 diabetic cardiomyopathy in mice. Free Radic Biol Med. 2013; 60:307-317.

64. 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.

65. McCracken E, Monaghan M, Sreenivasan S. Pathophysiology of the metabolic syndrome. Clin Dermatol. 2018; 36(1):14-20.

66. Kunitomo M, Yamaguchi Y, Kagota S, Otsubo K. Beneficial effect of coenzyme Q10 on increased oxidative and nitrative stress and inflammation and individual metabolic components developing in a rat model of metabolic syndrome. J Pharmacol Sci. 2008; 107(2):128-137.

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

68. Sourris KC, Harcourt BE, Tang PH, Morley AL, Huynh K, Penfold SA, et al. Ubiquinone (coenzyme Q10) prevents renal mitochondrial dysfunction in an experimental model of type 2 diabetes. Free Radic Biol Med. 2012; 52(3):716-723.

69. Raygan F, Rezavandi Z, Tehrani SD, 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):2357-2364.

70. Amin MM, Asaad GF, Abdel Salam RM, El-Abhar HS, Arbid MS. Novel CoQ10 antidiabetic mechanisms underlie its positive effect: Modulation of insulin and adiponectine receptors, Tyrosine kinase, PI3K, glucose transporters, sRAGE and visfatin in insulin resistant/diabetic rats. PLoS One. 2014; 9(2):e89169.

71. 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 Ther. 2015; 40(4):413-418.

72. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: Epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol. 2003; 91(6):2-8.

73. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37(27):2129-2200.

74. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg. 2016; 50(5):e1-e88.

75. Keith M, Geranmayegan A, Sole MJ, Kurian R, Robinson A, Omran AS, et al. Increased oxidative stress in patients with congestive heart failure. J Am Coll Cardiol. 1998; 31(6):1352-1356.

76. 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 Investig Med. 2015; 63(5):735-739.

77. Korantzopoulos P, Kolettis TM, Kountouris E. Inflammation and anti-inflammatory interventions in atrial fibrillation. Int J Cardiol. 2005; 104(3):361-362.

78. Tanaka T, Tsutamoto T, Nishiyama K, Sakai H, Fujii M, Yamamoto T, et al. Impact of oxidative stress on plasma adiponectin in patients with chronic heart failure. Circ J. 2007; 72(4):563-568.

79. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2):87-165.

80. Siregar S, Groenwold RH, de Mol BA, Speekenbrink RG, Versteegh MI, Brandon Bravo Bruinsma GJ, et al. Evaluation of cardiac surgery mortality rates: 30-day mortality or longer follow-up? Eur J Cardiothorac Surg. 2013; 44(5):875-883.

81. Spina S, Lei C, Pinciroli R, Berra L. Hemolysis and kidney injury in cardiac surgery: The protective role of nitric oxide therapy. Semin Nephrol. 2019; 39(5):484-495.

82. Zozina VI, Covantev S, Goroshko OA, Krasnykh LM, Kukes VG. Coenzyme Q10 in cardiovascular and metabolic diseases: Current state of the problem. Curr Cardiol Rev. 2018; 14(3):164-174.

83. Pechan I, Olejarova I, Danova K, Fischer V, Minarova H, Dobisova A, et al. Antioxidant status of patients after on-pump and off-pump coronary artery bypass grafting. Bratisl Lek Listy. 2004; 105(2):45-50.

84. Leong JY, van der Merwe J, Pepe S, Bailey M, Perkins A, Lymbury R, et al. Perioperative metabolic therapy improves redox status and outcomes in cardiac surgery patients: A randomised trial. Heart Lung Circ. 2010; 19(10):584-591.

85. Stone LH, Butterick TA, Duffy C, Swingen C, Ward HB, Kelly RF, 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):368-373.

86. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005; 366(9493):1267-1278.

87. Littarru GP, Langsjoen P. Coenzyme Q10 and statins: biochemical and clinical implications. Mitochondrion. 2007; 7(S1):S168-S174.

88. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. Jama. 2003; 289(13):1681-1690.

89. Passi S, Stancato A, Aleo E, Dmitrieva A, Littarru GP. Statins lower plasma and lymphocyte ubiquinol/ubiquinone without affecting other antioxidants and PUFA. Biofactors. 2003; 18(1-4):113-124.

90. Rundek T, Naini A, Sacco R, Coates K, DiMauro S. Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke. Archives of neurology. 2004; 61(6):889-892.

91. Schaefer WH, Lawrence JW, Loughlin AF, Stoffregen DA, Mixson LA, Dean DC, et al. Evaluation of ubiquinone concentration and mitochondrial function relative to cerivastatin-induced skeletal myopathy in rats. Toxicol Appl Pharmacol. 2004; 194(1):10-23.

92. Marcoff L, Thompson PD. The role of coenzyme Q10 in statin-associated myopathy: A systematic review. J Am Coll Cardiol. 2007; 49(23):2231-2237.

93. Banach M, Serban C, Ursoniu S, Rysz J, Muntner P, Toth PP, et al. Statin therapy and plasma coenzyme Q10 concentrations:A systematic review and meta-analysis of placebo-controlled trials. Pharmacol Res. 2015;99:329-36.

94. Paiva H, Thelen KM, Van Coster R, Smet J, De Paepe B, Mattila KM, et al. High-dose statins and skeletal muscle metabolism in humans: A randomized, controlled trial. Clin Pharmacol Ther. 2005; 78(1):60-68.

95. Stocker R, Pollicino C, Gay CA, Nestel P, Colquhoun D, Whiting M, 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.

96. Choi H-K, Won E-K, Choung S-Y. Effect of Coenzyme Q(10) supplementation in statin-treated obese rats. Biomol Ther. 2016; 24(2):171-177.

97. Silver MA, Langsjoen PH, Szabo S, Patil H, Zelinger A. Effect of atorvastatin on left ventricular diastolic function and ability of coenzyme Q 10 to reverse that dysfunction. Am J Cardiol. 2004; 94(10):1306-1310.

98. Caso G, Kelly P, McNurlan MA, Lawson WE. Effect of coenzyme q10 on myopathic symptoms in patients treated with statins. Am J Cardiol. 2007; 99(10):1409-1412.

99. Young JM, Florkowski CM, Molyneux SL, McEwan RG, Frampton CM, George PM, et al. Effect of coenzyme Q(10) supplementation on simvastatin-induced myalgia. Am J Cardiol. 2007; 100(9):1400-1403.

100. Skarlovnik A, Janić M, Lunder M, Turk M, Šabović M. Coenzyme Q10 supplementation decreases statin-related mild-to-moderate muscle symptoms: A randomized clinical study. Med Sci Monit. 2014; 20:2183-2188.

101. Digiesi V, Cantini F, Oradei A, Bisi G, Guarino G, Brocchi A, et al. Coenzyme Q10 in essential hypertension. Mol Aspects Med. 1994; 15:s257-s263.

102. 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.

103. Fabre Jr LF, Banks RC, McIsaac WM, Farrell G. Effects of ubiquinone and related substances on secretion of aldosterone and cortisol. Am J Physiol. 1965; 208(6):1275-1280.

104. Hargreaves IP, Duncan AJ, Heales SJ, Land JM. The Effect of HMG-CoA reductase inhibitors on coenzyme Q 10. Drug Saf. 2005; 28(8):659-676.

105. Mohr D, Stocker R. Radical-mediated oxidation of isolated human very-low-density lipoprotein. Arterioscler Thromb. 1994; 14(7):1186-1192.