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Original article

COENZYME Q_{10} AND CARDIOVASCULAR SYSTEM

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Abstract*

Aim. CoQ10 (Ubiquinone-10) is a compound which serves as coenzyme in key enzymatic reactions during the energy production in the cell, may be found in each cell in different amounts, has the lipid structure and is similar to vitamin. Although it resembles vitamins in structure, it is not classified as vitamin due to the fact that it can be synthesized in the body. CoQ10 can be used as a protective and auxiliary substance in some diseases and treatment for its existence in all cells, having electron carrier feature in electron transport chain and strong antioxidant function.

The CoQ10 deficiency are available in cases such as cardiac failure, angina pectoris, cardiomyopathy, hypertension, mitral valve prolapsus and atherosclerosis. CoQ10 supplement provides improvement in dilatation based on endothelium by regulating the vascular tonus. CoQ10 can prevent endothelial biomolecules from being damaged by inhibiting the lipid and protein peroxidation thanks to the antioxidant function, apart from the indirect effect on realization of vasodilatation. Moreover, It is reported that CoQ10 provides improvement in treatment of congestive cardiac failure, stroke volume, ejection fraction, cardiac output, cardiac index and diastolic volume index. Diastolic dysfunction is a myocardial insufficiency which constitutes the half of cardiac failure cases. In the studies about diastolic dysfunction, the results show that results show that CoQ10 may be administered as reliable, effective and complementary treatment method. Hypertension is the non-physiological elevation of systemic blood pressure. It is reported that action mechanism of CoQ10 in reducing the blood pressure occurs through the protection of NO concentration in endothelium. Further, it was noted that important improvements were observed following CoQ10 administration in patients having low extracellular SOD levels and high oxidative stress such as coronary artery diseases, and improvement in oxidative stress, decrease in peroxynitrite level, development in vasodilatation and decrease in myocardial damage were encountered. CoQ10 decreases blood viscosity in patients with ischemic cardiac disease and increases stream of blood into cardiac muscles.

Conclusion. The studies suggest that CoQ_{10} supplements can be used as a safe and effective treatment method for cardiovascular diseases as ischemic cardiomyopathy, hypertensive, valvular heart disease, stroke volume, ejection fraction, cardiac output and diastolic dysfunction.

Keywords **:** Coenzyme, CoQ_{10}, Cardiovascular System

Introduction

CoQ10 is a substance which was firstly isolated from mitochondria of cattle heart by Dr. Frederick Crane in 1957, whose chemical structure was determined and which was synthesized with fermentation (Pepe et al., 2007).

Q symbolizes the quinone group in its structure and 10 figure symbolizes the 10 isoprene units, each of which bears 5 carbons in the side chain. Trans-polyisoprene provides affinity against inner part of cell membrane. 2 methoxy groups play a role in enzyme activity such as methyl group (Overvad et al., 1999, Bhagavan et al., 2007). Since it has a quinone structure, it is also called as Ubiquinone (Hathcock and Shao, 2006). Ubiquinone word was derived from "ubiquitos quinone" words and it is a term which is associated with its existence in all cells and means "ubiquitos" (Overvad et al., 1999).

CoQ10 (Ubiquinone-10) is a compound which serves as coenzyme in key enzymatic reactions during the energy production in the cell, may be found in each cell in different amounts, has the lipid structure and is similar to vitamin. Although it resembles vitamins in structure, it is not classified as vitamin due to the fact that it can be synthesized in the body (Overvad et al., 1999, Bhagavan and Chopra, 2006, Stocker, 2007). CoQ10 may be found in three different forms in the biological tissues; oxide ubiquinone form (CoQ10), partially-reduced semiquinone form (free radical by-product) and fully-reduced ubiquinoal form ($CoQH_2$) (Gürkan and Dündar 2005, Molyneux et al. 2008, Parkhideh 2008, Ercan and Nehi,r 2010).

Usage and/or Application Areas of Coenzyme Q10

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CoQ10 can be used as a protective and auxiliary substance in some diseases and treatment for its existence in all cells, having electron carrier feature in electron transport chain and strong antioxidant function. In the studies conducted, its therapeutic properties have been observed in cardiovascular diseases, diabetes mellitus and neurodegenerative disorders. For this reason, it is suggested that its use as a supplement and support substance will provide many benefits for the body, excluding its intake into the body with basic nutrition elements (Overvad et al. 1999, Kavas et al. 2006).

Effects of Coenzyme Q10 on Cardiovascular System

It is reported that findings regarding the CoQ10 deficiency are available in cases such as cardiac failure, angina pectros, cardiomyopathy, hypertension, mitral valve prolapsus and atherosclerosis (Singh et al. 1998).

Possible effect ways of CoQ10 in treatment of cardiovascular diseases or minimization of the risk of catching such diseases are as follows:

- Showing antioxidant effect
- Increasing the cardiac energy production
- Playing indirect role in endothelial-induced vasodilatation
- Providing vascular membrane stabilization (reducing plasma cholesterol level and inhibitor effect on LDL oxidation)
- Anti-viscosity effect in the plasma. (Greenberg and Frishman, 1990)

CoQ10 and endothelial function

Endothelial homeostasis is based on the balance between biological events and some mutual functions.Nitric oxide (NO) produced by endothelial cells is also accepted as a free radical since it has un conjugated electron. Besides, while other free radicals are harmful for the cells in every concentration, NO has very important physiological functions in low concentrations. Nitric oxide is a anti-atherosclerotic substance having a role in many vital events such as physiological regulation of vascular tonus, inhibition of platelet aggregation, prevention of leukocyte adhesion to endothelium, clearing of free oxygen radicals, continuity of normal vascular permeability, prevention of smooth muscle proliferation and regeneration of endothelium cells (Lowenstein et al., 1994, Guo et al., 1996, Lefer and Lefer, 1996). Endothelial NO is playing a role either in systemic vasodilatation or regulation of blood pressure by providing local vasodilatation in heart, brain, liver and gastrointestinal systems (Snyder 1992, Lowenstein et al., 1994, Loscalzo and Welch, 1995). This effect of NO starts with activation of guanylate cyclase in endothelial smooth muscle cells, guanylate cyclase increases the cGMP formation that is the secondary messenger from GTP and it ultimately shapes the vasodilatation (Snyder, 1992, Lowenstein et al., 1994).

In the studies conducted in this regard, it was reported that endothelial-induced extracellular superoxide dismutase (ecSOD) activity decreases in patients having coronary artery disease, CoQ10 supplement provides improvement in dilatation based on endothelium by regulating the vascular tonus. It is suggested that this effect of CoQ10 is not direct; since it reacts with free radicals and it reduces them by means of NO which is made available in adequate density in the environment, NO whose reaction with free radicals is prevented or restricted plays a positive role in endothelial relaxation (Tiano et al., 2007, Belardinelli et al., 2008).

CoQ10 can prevent endothelial biomolecules from being damaged by inhibiting the lipid and protein peroxidation thanks to the antioxidant function, apart from the indirect effect on realization of vasodilatation (Yamashita and Yamamoto 1997, Götz et al., 2000, Crane, 2001, Turunen et al., 2004, Bonakdar and Guarneri, 2005, Gürkan and Dündar, 2005, Bentinger et al., 2007, Kumar et al., 2009).

Again in different studies conducted; it is reported that CoQ10 inhibits LDL (low density lipoprotein) oxidation (Yokoyama et al. 1996), reduces lipid hydroperoxide concentration and decelerates the development of atherosclerotic lesions in aorta (Littarru and Tiano, 2007).

Masaru et al. (2008) stated that CoQ10 application corrects endothelial dysfunction in mesenteric arteries by weakening the oxidative and nitrative stress in a dose dependent manner, it may be effective in reducing the cardiovascular risks thanks to its antioxidant property.

CoQ10 and Cardiac failure

It was found that CoQ10 levels of patients who have chronic cardiac failure are too low both in tissue and serum samples (Folkers et al. 1985, Kumar et al. 2009).

In the study conducted by Langsjoen et al. (1994); it is reported that long-term (8 years) CoQ10 supplement (75 mg- 600mg/day) administered on 424 patients having disorders related with heart such as ischemic cardiomyopathy, diastolic dysfunction, hypertensive cardiac disease and valvular cardiac disease provided important improvements in myocardial functions, no adverse effect was not

encountered in the patients and CoQ10 can be used as a safe and effective auxiliary therapeutic method in cardiovascular diseases.

It is reported that CoQ10 provides improvement in treatment of congestive cardiac failure, stroke volume, ejection fraction, cardiac output, cardiac index and diastolic volume index (Soja and Mortensen, 1997, Sander et al., 2006).

In a long-term study conducted on 143 patients with cardiomyopathy and in which daily 100 mg CoQ10 supplement was administered in patients, clinical states and myocardial functions of patients were followed for 6 years. In the end, it was determined that elevation was seen in ejection fraction rates of 84% of patients in the rate of 44-60% (Langsjoen, 1990).

It is noted that proinflammatory mediators such as IL-6 and TNF-alpha play an important role in development of congestive cardiac failure and acute myocardial infarction. In a study conducted within this scope, daily 270 mg ubiquinol was administered on 31 patients with cardiac failure for 12 weeks together with carnitine, decrease was observed in IL-6 and TNF-alpha levels in the treatment group at the end of the treatment. This situation was explained in such way that " CoQ10 caused change in immunity response" (Kumar et al., 2007).

CoQ10 and diastolic dysfunction

Diastolic dysfunction is a myocardial insufficiency which constitutes the half of cardiac failure cases. It is a scene characterized by inadequate left ventricular filling. One of the most important reasons in development of diastolic dysfunction is left ventricle hypertrophy. This condition causes pulmonary venous hypertension and diastolic cardiac failure syndromes.

There is a need for adequate ATP for separating myosin from actin during the diastole in order to fulfill the normal diastolic function. ATP provides calcium to be released from troponin C and to be retaken by SR actively. Diastolic dysfunction may occur in cases where absolute ADP and Pi concentration or relative ADP/ATP rate increased. It is stated that this abnormalities observed in energy factors may be resulted from the inability of converting ADP into ATP adequately due to low phosphocreatine levels (Apstein and Morgan, 1994, Ingwall, 1998, Kumar et al., 2009).

In a study in which effects of CoQ10 in diastolic dysfunction was examined, daily 200 mg CoQ10 supplement was administered on patients treated for 14,5 months on average and important positive improvements were observed. In the said research, while it was noted that decrease was seen in interventricular wall thickness, it was stated that no patient had ventricular tachycardia in the treatment group (Kumar et al., 2007).

In similar studies, it is noted that significant decrease in again interventricular septal thickness (Langsjoen et al., 1997) and myocardial thickness and improvement in diastolic dysfunction was observed (Langsjoen and Folkers, 1993). These results show that CoQ10 may be administered as reliable, effective and complementary treatment method.

Role of CoQ10 in hypertension

Hypertension is the non-physiological elevation of systemic blood pressure. It is defined as systolic blood pressure above 140mmHg and diastolic blood pressure above 90 mmHg in resting (Donald et al., 2005). Hypertension is a complicated disease developing with genetic factors and some pathophysicological processes and/or adverse environmental impacts (Bilir et al., 2003, Donald et al., 2005).

It is reported that action mechanism of CoQ10 in reducing the blood pressure occurs through the protection of NO concentration in endothelium. Reactive oxygen types formed in vascular system cause decrease in NO concentration (NO combines with superoxide and provides peroxynitrite to be produced. CoQ10 provides NO to be protected by allowing reactive oxygen types formed to be swept out. Thus, as a result of this condition, it is protected from attack of reactive oxygen types thanks to vasodilatation induced by NO. With this aspect, CoQ10 works with a different mechanism than other anti-hypertensive agents. Since it has no important adverse effect, it undertakes a potential and useful clinical role as an adjuvant and alternative treatment in treatment of hypertension (Kumar et al. 2009).

In a meta-analysis study which has been conducted since 1975 and in which 12 studies are present, it was reported that average 17 mmHg decrease in systolic blood pressure and 10mmHg decrease in diastolic blood pressure was provided without any adverse effect (Rosenfeldt et al., 2007). In hypertensive cardiac diseases, it was observed that CoQ10 administration caused decrease in high blood pressure in rate of 80% (Langsjoen and Folkers, 1993). At the end of research in which 60 mg CoQ10 supplement was orally administered in the patients whom antihypertensive treatment was applied for two times a day for 8 weeks, decrease in systolic and diastolic blood pressure and increase in HDL cholesterol, vitamin A, C, E and beta-carotene levels were found in patients (Singh et al., 1998).

Role of CoQ10 in ischemic cardiac diseases

The inability of covering the need of organ or tissue to oxygen and other metabolites by the circulation and the inability of keeping residuals formed away are defined as "ischemia". Reperfusion is restoring the blood circulation is ischemic tissue.

Cellular dysfunction and necrosis develop depending on depletion of cellular energy sources and accumulation of toxic metabolites as a result of chemical reactions started in the tissues exposed to ischemia. Blood stream is required to be provided again for regeneration of cells in ischemic tissue and clearance of toxic metabolites. Nevertheless, reperfusion of ischemic tissue leads to increase of tissue damage paradoxically and damage formed is much bigger and more important in the reperfusion period compared with the ischemic period (Zimmerman and Granger, 1992, Majino and Jorris, 1995).

While reperfusion of ischemic tissue covers the oxygen and other metabolic requirements of the tissue on one hand, some reactions increase the tissue damage paradoxically (Zimmerman and Granger, 1992). There are formation of either endothelium cell-derived or neutrophile-derived free oxygen radicals, reduction of NO level due to peroxy nitrite formation, neutrophile activation and cytokines released by macrophages (Tumor Necrosis Factor, Interleukin-1,2,6 and 8) (Baud and Ardaillou, 1993, Weight et al., 1996, Akçetin et al., 1999).

It was noted that important improvements were observed following CoQ10 administration in patients having low extracellular SOD levels and high oxidative stress such as coronary artery diseases, and improvement in oxidative stress, decrease in peroxynitrite level, development in vasodilatation and decrease in myocardial damage were encountered (Belardinelli et al. 2008).

Tsuneki et al. (2007) reported that CoQ10 decreases endothelial cell deaths by minimizing the inflammatory cytokines and can be used as an auxiliary element in ischemic cardiac diseases.

It was noted that CoQ10 decreases blood viscosity in patients with ischemic cardiac disease and increases stream of blood into cardiac muscles (Kato and Yoneda, 1990).

Conclusion

The studies suggest that CoQ_{10} supplements can be used as a safe and effective treatment method for cardiovascular diseases as ischemic cardiomyopathy, hypertensive, valvular heart disease, stroke volume, ejection fraction, cardiac output and diastolic dysfunction.

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