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COENZYME Q_{10}

KOENZİM Q_{10}

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ABSTRACT

Coenzyme Q_{10} (CoQ_{10}) is an essential cofactor of the electron transport chain which plays a pivotal role to supply energy for chemical reactions in the body, and a lipophilic antioxidant component of the lipid membranes that surround all cells and the various organelles such as microsomes and mitochondria. Even though the antioxidants are produced by the body, their blood level is reduced by aging, lifestyle and environmental factors. As a well-established antioxidant, CoQ_{10} participates in electron and proton transport of the respiratory chain in the mitochondrial inner membrane and decreases oxidative stress and prevents free radical oxidation of the cells and tissues. In number of trials, potential usefulness of CoQ_{10} have been shown in mitochondrial disorders and variety of diseases progressed by due to oxidative stress and decreased antioxidant capacity. We have explored CoQ_{10}'s cellular bioenergetic activity and antioxidant properties, and its functions for common clinical conditions such as cardiovascular and neurodegenerative diseases, cancer, diabetes, and renal failure in our examination.

Key Words: *Coenzyme Q_{10}, ubiquinone, antioxidant, mitochondrial disorders.*

ÖZET

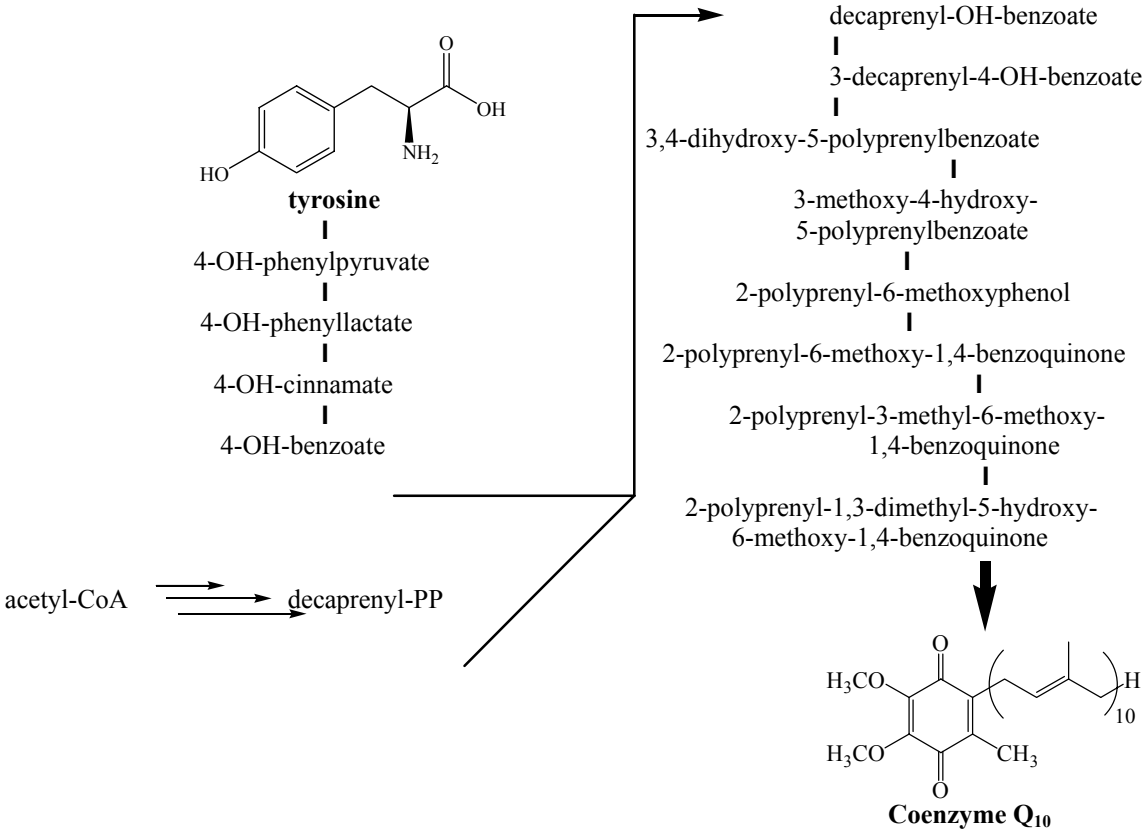
Koenzim Q_{10} , vücuttaki kimyasal reaksiyonlara enerji sağlanmasında önemli rol oynayan elektron taşıma zincirinin esansiyel bir kofaktörü, mikrozom, mitokondri gibi çeşitli organelleri ve hücreleri çevreleyen lipid membranların bileşeni olan lipofilik bir antioksidandır. Antioksidanlar vücut tarafından

üretilmelerine rağmen, kandaki seviyeleri yaşlanma, yaşam tarzı ve çevresel faktörlerle azalmaktadır. Koenzim Q_{10} , iyi bir antioksidan olarak mitokondriyal iç membranındaki solunum zincirinin elektron ve proton transportuna katılır ve oksidatif stresi azaltarak, hücre ve dokularda serbest radikal oksidasyonunu önler. Koenzim Q_{10}'un oksidatif strese ve azalmış antioksidan kapasiteye bağlı olarak ilerleyen çeşitli hastalıklardaki ve mitokondriyal düzensizliklerdeki potansiyel yararlılığı bir çok çalışmada gösterilmiştir. Biz bu çalışmamızda, koenzim Q_{10}'un hücresel biyoenerjik aktivitesi ve antioksidan özellikleri ile kardiyovasküler hastalıklar, nörodejeneratif hastalıklar, kanser, diyabet ve böbrek yetmezliği gibi klinik durumlardaki fonksiyonlarını araştırdık.

Anahtar kelimeler: *Koenzim Q_{10} , ubikinon, antioksidan, mitokondriyal bozukluklar.*

INTRODUCTION

Coenzyme Q_{10} (CoQ_{10}, ubiquinone, vitamin Q_{10}, ubidecaquinone or ubidecarenone), a vitamin-like benzoquinone compound synthesized naturally in the human body, is vital in the production of energy in processes which are aerobic respiration, aerobic metabolism or cell respiration. It was first isolated from the mitochondria of bovine hearts in 1957 (1) and its chemical structure was identificated and synthesis was completed in 1958 (2).



Scheme 1: Biosynthesis steps of CoQ_{10}

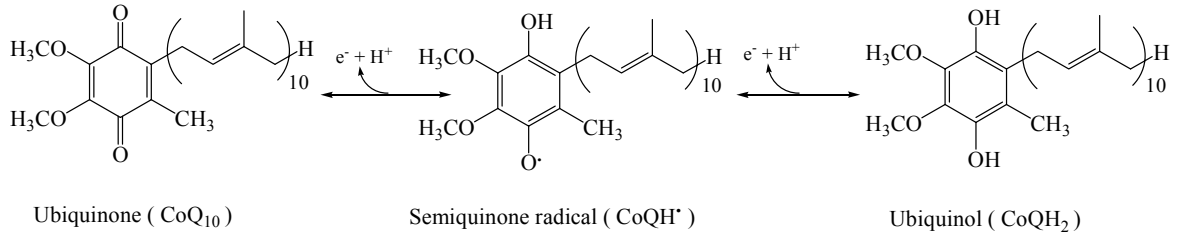
Chemistry and Biosynthesis

CoQ_{10} belongs to a family of compounds known as ubiquinones. All animals and humans, can synthesize ubiquinones, so CoQ_{10} cannot be considered a vitamin (3). Ubiquinones are fat-soluble molecules with anywhere from 1 to 12 isoprene units. The ubiquinone found in humans, CoQ_{10}, has a 10 isoprene side units attached to its 1,4-benzoquinone (4), structurally similar to vitamin K (5). The total body content of CoQ_{10} has been estimated to be 0.5–1.5 g, its active form protein bound. Normal blood levels range from 0.7–1.0 µg/mL. It is found in relatively higher concentrations in cells with high energy requirements such as heart, liver, muscle and pancreas. Human cells synthesize CoQ_{10} from tyrosine in an aromatic pathway, requiring sufficient levels of vitamins such as folic acid, niacin, riboflavin and pyridoxine (6). The biosynthesis of CoQ_{10} results from the condensation of parahydroxybenzoate ring, arising from tyrosine of phenylalanine, with a 10-isoprenoid chain (see **Scheme 1**) (7).

Mechanism of Action and Antioxidant Function of CoQ_{10}

CoQ_{10} is highly soluble in lipids and is found in almost all cell membranes, as well as lipoproteins. CoQ_{10}, found in the mitochondrial inner membrane, is the cofactor for at least three mitochondrial enzymes, complexes I, II and III, that play a pivotal role in oxidative phosphorylation. Oxidative phosphorylation consists of five protein-lipid enzyme complexes located in the inner mitochondrial membrane which include flavins, quinoid compounds (CoQ_{10}) and transition metal compounds (Fe-S clusters, hemes, protein-bound copper). These enzymes are stated complex I (NADH:ubiquinone oxidoreductase), complex II (succinate:ubiquinone oxidoreductase), complex III (ubiquinol:ferrocytochrome C oxidoreductase), complex IV (ferrocytochrome c:oxygen oxidoreductase or cytochrome C oxidase), and complex V (ATP synthase). CoQ_{10} functions as the unique non-protein component of the electron transport chain (ETC) not being attached to a protein itself. This unique characteristic enables CoQ_{10} to move and transfer electrons between flavoproteins, the various dehydrogenases and cytochrome segments of the mitochondrial respiratory chain (MRC). CoQ_{10} is considered the central rate-limiting component of the MRC and each pair of electrons processed by the ETC must first interact with CoQ_{10}. CoQ_{10} accepts electrons from reducing equivalents generated during fatty acid and glucose metabolism and transfers them to electron acceptors. At the same time, creating a proton gradient across the inner mitochondrial membrane, it transfers protons outside that membrane. The energy released when the protons flow back into the mitochondrial interior is used to produce ATP. Therefore, CoQ_{10} plays an essential role in ATP production (4,7-12).

The ability of the benzoquinone group of CoQ_{10} to accept and donate electrons is a critical feature in its physiological functions. CoQ_{10} can exist in three oxidation states (see **Scheme 2**): the fully oxidized ubiquinone form (CoQ_{10}), the free-radical semiquinone intermediate ($CoQH\cdot$), and the fully reduced ubiquinol form ($CoQH_2$) (13).



Scheme 2: Oxidation states of CoQ_{10}

As an antioxidant, it scavenges free radicals and acts to inhibit lipid and protein peroxidation. CoQ_{10} constantly undergoes oxidation-reduction recycling (14). The reduced form, $CoQH_2$ acts also as a lipophilic antioxidant and participates in electron and proton transport of the MRC. It gives up electrons to neutralize oxidants and displays its strongest antioxidant activity. Thus, a changing in CoQ_{10} redox state may reflect a change in membrane electron transport and the effectiveness of protection against toxic reactive oxygen species (ROS) such as hydrogen peroxide and superoxide radical (15-17). Its redox status controls the equilibrium between the reducing activities of the different dehydrogenases (18). Some investigators have documented that CoQ_{10} prevents lipid peroxidation at nearly the same rate as vitamin E (19). The ubiquinol content of LDL is an important factor in their resistance to peroxidation (20). It was found that CoQ_{10} to be more efficient in preventing LDL oxidation than α-tocopherol, lycopene, or ß-carotene (21). In addition, CoQ_{10} can work synergistically with α-tocopherol, regenerating its active form, in the same mechanism as with vitamin C. CoQ_{10} can be regenerated to its active form in the body. However, tissue levels of CoQ_{10} have been reported to decline with age (22).

The membrane stabilizing property of CoQ_{10} has been postulated to involve the phospholipid-protein interaction that increases prostaglandin metabolism. CoQ_{10} stabilizes myocardial calcium-dependent ion channels and prevents the consumption of metabolites essential for ATP synthesis (5). CoQ_{10} reduces blood viscosity, and improves blood flow to cardiac muscle in patients with ischemic heart disease (23).

In a human study it was investigated that the dietary CoQ_{10} supplementation resulted in a higher plasma level of $CoQH_2$ in 22 subject (24). The ratio of $CoQH_2$ to CoQ_{10} which was

suggested an index of oxidative stress (20) is about 95/5 in human plasma from healthy donors (25). The effect of an oral dose of 90 mg/day CoQ_{10} on the antioxidative status in 22 healthy young subjects was investigated before and after induction of an oxidative stress by fish oil supplementation. The total amount of plasma CoQ_{10} increased significantly from 0.7 ± 0.1 mumol/l before supplementation to 1.7 ± 0.3 mumol/l after one week of supplementation while the redox status (reduced CoQ_{10}/total CoQ_{10}) remained constant, even during a following fish oil supplementation (26).

The whole contribution of ubiquinol to antioxidant defence *in vivo* is uncertain. It may be important in mitochondria, where the ETC can easily re-oxidize / re-reduce $CoQH^{\cdot}$. The enzyme DT-diaphorase can reduce CoQ_{10} to $CoQH_2$ and this was suggested to be part of its antioxidant function *in vivo* (20).

As a cutaneous antioxidant, CoQ_{10} has the efficacy to prevent many of the detrimental effects of photoaging. CoQ_{10} penetrated into the epidermis and reduce the level of oxidation measured by weak photon emission. CoQ_{10} was shown to be effective against UVA mediated oxidative stress in human keratinocytes in terms of thiol depletion, suppression the expression of collagenase in human dermal fibroblasts following UVA irradiation, activation of specific phosphotyrosine kinases, reduction in wrinkle depth and prevention of oxidative DNA damage (27).

Prooxidant effects of CoQ_{10}

The role of CoQ_{10} in free oxyradical formation and as an antioxidant remains controversial. Demonstration of the existence of the $CoQH^{\cdot}$ during electron transport suggests that the highly reactive $OH^{\cdot}$ radical may be formed from the ubisemiquinone. In addition, the Fe-S species as the source of ETC produce free radical. The unpaired electron of the $CoQH^{\cdot}$ most likely dismutases superoxide radicals. Transfer of the odd electron to H_2O_2 resulted in $HO^{\cdot}$ and HO- formation by homolytic cleavage. A similar reaction was also possible with lipid hydroperoxides accumulate in biological membranes during lipid peroxidation. The reaction products emerging from this reaction were alkoxy radicals. Both $HO^{\cdot}$ and alkoxy radicals are strong initiators and promoters of lipid peroxidation (28,29).

CLINICAL USES OF CoQ_{10}

Cardiovascular Disease (CD)

Various clinical trials have supported the use of CoQ_{10} in the prevention and treatment of several disorders related to oxidative stress. It has been demonstrated that antioxidant properties and central role of CoQ_{10} in mitochondrial oxidative phosphorylation make it useful as adjunctive therapy for cardiovascular diseases leading to CoQ_{10} deficiency include congestive heart failure, cardiomyopathy, angina pectoris, coronary artery disease, hypertension, mitral valve prolapse, coronary revascularization, chronic obstructive pulmonary disease (COPD). Heart tissue biopsies in patients with various heart diseases showed a CoQ_{10} deficiency in 50-75% of cases due to the fact that there is more CoQ_{10} in the heart tissue than in any other muscle in the body (30-32). Most of the investigations have focused on CoQ_{10} as a treatment for CD. In a clinical study of 424 patients with various forms of CD over an 8-year period, researchers reported that CoQ_{10} is a safe and effective adjunctive treatment for a broad range of CD (33).

Congestive Heart Failure (CHF): The presence of increasing symptoms associated with CHF has been correlated to the severity of CoQ_{10} deficiency. CoQ_{10} myocardial tissue levels in CHF patients are on average 33% lower than in control patients (34,35). The degree of CoQ_{10} deficiency correlated with the severity of symptoms and presence of dilated cardiomyopathy. In a study made on 94 patients over 50 years of age, patients exhibiting a significantly lower serum free cholesterol-related CoQ_{10} value had an increased risk of CHF (36).

The researchers studied the efficacy of 50–150 mg/day of CoQ_{10} as adjunctive therapy in a study of 2359 patients with heart failure in New York Heart Association (NYHA) Class II or III stabilized on conventional therapy. After three months, patients receiving CoQ_{10} improved functionally and that patients in NYHA Class II showed better improvement rates than did patients in NYHA Class III (37). In another experiment, the efficacy of 100 mg/day of CoQ_{10} as adjunctive treatment in CHF of various origins was evaluated in 35 patients who were symptomatic on conventional therapy. Two thirds of the patients responded with an improvement in functional class by one or two scores. The most declared response was in the dilated cardiomyopathy group and the least valuable effects were in the ischemic heart disease group (38). It was also investigated CoQ_{10} receives a well-documented role as an adjunctive treatment of CHF using a meta-analysis method which is used to measure the changes in the cardiac parameters (39). These findings led to several clinical studies that examined the efficacy of CoQ_{10} as adjunctive therapy for treating CHF.

CoQ_{10}'s proposed mechanism on benefiting CHF is through positive inotropic action which increases the contractile force of the heart to improve cardiac output. Failed hearts are believed to

failure ATP (5). The heart muscle may become ischemic as the result of myocardial infarction (MI) or during cardiac surgery. Increased generation of ROS when the heart muscle's oxygen supply is restored is thought to be an important contributor to myocardial damage occurring during ischemia-reperfusion. Pretreatment of animals with CoQ_{10} has been found to decrease myocardial damage due to ischemia-reperfusion (40,41).

Angina: CoQ_{10} has been shown to be effective in the treatment of angina. In a study, patients with specific types of angina inclined to have more active oxygen forms by leukocytes, higher concentration of malonic dialdehyde in plasma and lower antiperoxide resistance of plasma. By combining CoQ_{10} with antianginal therapy, the generation of free radicals were suppressed by leukocytes, allowing antiperoxide plasma resistance to increase (42). In a trial of 12 adults with stable angina on conventional therapy, 150 mg/day of CoQ_{10} for four weeks showed a decrease in both anginal frequency and use of nitroglycerin ($p>0.05$) (43).

Hypertension: CoQ_{10} is used as a treatment for high blood pressure for 40 years. In the United States, 109 patients with symptomatic essential hypertension were observed after adding CoQ_{10} to their antihypertensive drug therapy. After slightly more than 4 months of using CoQ_{10}, 51% of patients could stop taking antihypertensive drugs (44).

The benefits of CoQ_{10} in hypertensive patients with deficiencies of succinate dehydrogenase and CoQ_{10} reductase activity were investigated. Improving bioenergetics by repleting CoQ_{10} deficiency states may reduce blood pressure. After repletion of CoQ_{10} stores, they reported an increase in the specific activity of CoQ_{10} with reductions in systolic and diastolic pressure (45,46). In a trial, 20 hypertensive subjects with low serum CoQ_{10} concentrations exhibited significant reductions in systolic and diastolic blood pressure from the administration of 33.3 mg doses of CoQ_{10} three times daily compared to placebo group (5).

In a study of hypertensive patients suffering from coronary artery disease (CAD), the effects on blood pressure and insulin resistance of 60 mg doses of CoQ_{10} in twice daily are investigated. After 8-week period, reductions were reported in systolic and diastolic blood pressure, lipid peroxidase, fasting and two-hour plasma insulin, blood glucose, and serum triglyceride levels. An increase in high density lipoprotein (HDL)-cholesterol and vitamins A, C, and E, and beta carotene serum concentrations in the CoQ_{10} treated group were observed, as well (47). Researchers studied the antihypertensive effects of 50 mg doses of CoQ_{10} in twice daily in 26 patients with essential hypertension. After 10 weeks, both diastolic and systolic blood pressure were significantly reduced

($p<0.001$), serum CoQ_{10} concentrations were increased, serum total cholesterol decreased and serum HDL-cholesterol increased significantly (48).

Atherosclerosis: Antioxidant therapy with CoQ_{10} in doses of 3 mg/ kg daily was suggested to be used as an auxiliary to lipid lowering for beneficials effects related to characteristics of atheroma independent of hypolipidemic agents (49).

Sudden Heart Failure: In a trial, it was found CoQ_{10} can provide rapid protective effects in patients with acute myocardial infarction (sudden heart failure) if administered within three days of the onset of symptoms (50).

Surgery-Induced Stress: Additional to reducing the effects of oxidative stress CoQ_{10} has the potential to improve energy production in mitochondria by bypassing defective components in the MRC. CoQ_{10} pretreatment could improve the recovery of the myocardium after stress (51).

Cardiomyopathy: It was stated given CoQ_{10} in doses 300 to 400 mg daily to patients with CHF and cardiomyopathy. By boosting the energy output of heart cells, CoQ_{10} makes damaged heart muscles stronger and better able to pump blood (52). CoQ_{10} had shown to be deficient in myocardial tissue biopsies taken from dilated cardiomyopathy (DC) hearts. Researchers demonstrated that CoQ_{10} therapy is potentially useful in the treatment of children with idiopathic DC (53). Usefullness of CoQ_{10} as an adjunct to conventional therapy in pediatric cardiomyopathy also demonstrated (54). It was studied the long-term efficacy and safety of CoQ_{10} therapy for idiopathic DC in 126 symptomatic patients received 33.3 mg CoQ_{10} three times daily over 6 years additional to their traditional therapy. Survival rates at 1, 2, 3, 4, and 5 years were 97%, 84%, 79%, 70%, and 57%, respectively (55).

In Open Heart Surgery / Arrhythmias: CoQ_{10} is also used in open-heart surgery to obtain myocardial protection. In a study, 40 patients undergoing coronary artery bypass graft received either CoQ_{10} 150 mg daily for 7 days prior to surgery or a placebo. The serum concentrations of post-operative markers of oxidative damage in the treatment group and the incidence of ventricular arrhythmias were significantly lower ($p<0.05$) than in the control group during the recovery period (56). In a placebo-controlled study, it was showed that the administration of CoQ_{10} may improve surgical recovery and lessen the magnitude of surgical insult in heart surgery (57).

With cholesterol Lowering Statin Drugs: It was reported patients who take cholesterol lowering drugs, which block the synthesis of CoQ_{10} inducing CoQ_{10} deficiency in the heart muscle, should make strong their heart with supplemental CoQ_{10} (58).

Doxorubicin Cardiotoxicity Prophylaxis: Doxorubicin (Adriamycin) which is an anthracycline used in cancer chemotherapy inhibits CoQ_{10}-dependent enzymes. CoQ_{10} may have a potential role in the prevention of doxorubicin-induced cardiotoxicity. Pretreatment with CoQ_{10} may decrease its cardiotoxic effects by inhibiting of doxorubicin-induced lipid peroxidation and scavenging free radicals (5). The researchers studied the early detection of cardiotoxicity in doxorubicin-treated patients with cancer, using 50 mg doses of CoQ_{10} daily. The mean systolic interval improved or shortened, with increasing cumulative doses of doxorubicin (200–500 mg/m^2), resulting in a decreased incidence of cardiac dysfunction (59).

Immune Modulation

Studies have demonstrated the degree of CoQ_{10} deficiency is correlated with the severity of immune compromised diseases. Patients with AIDS showed significant lower CoQ_{10} serum concentrations than AIDS-related complex patients, who had lower levels than healthy subjects (60). Deficiency levels of CoQ_{10} in HIV-infected individuals play a role in symptoms. Asymptomatic patients showed low levels of deficiency, while AIDS patients increased in deficiency (61).

Research of CoQ_{10} and the human immune system in patients with cardiovascular problems, cancer and diabetes found that, 60 mg of CoQ_{10} daily for 3-12 weeks significantly raised their IgG levels, an antibody which supports immune function (62). In a clinical condition of 8 adult patients treated with 60 mg of CoQ_{10} daily it was reported significant increases in serum IgG levels over 1–4 months (63). CoQ_{10} stimulates immune system, causing augmented resistance to infection (64), higher antibody levels, greater numbers and/or activities of macrophages and T lymphocytes (65,66), and. CD4 and CD8 are proteins found on the surface of T cells, CD4 to CD8 T-cell ratios decreased in cancer patients (67). A study of 14 healthy adults treated with 100 mg/day of CoQ_{10} for 2 months showed significant increases in CD4/CD8 T-cell ratios, indicating stimulation of the immune system (68).

Cancer

Research has shown a possible connection between CoQ_{10} deficiency and both carcinomas and non-malignant lesions (69). Blood levels of CoQ_{10} are frequently reduced in cancer patients, supplementation with this compound has been tested in patients undergoing traditional treatment. Lots of studies have stated the incidence of CoQ_{10} deficiency in a type of cancers including breast, lung, pancreatic, prostate, and colon cancer (70-73). In a trial of 32 breast cancer patients with metastases to axillary lymph nodes, 90 mg./day of CoQ_{10} plus high-dose antioxidant therapy with

ascorbic acid, α-tocopherol, beta carotene, selenium, and omega-3 and omega-6 fatty acids were given in addition to surgery and chemotherapy. During the 18-month study period, none of the patients showed signs of further metastases and 6 of the 32 patients had partial tumor regression (74,75).

In a follow-up study, one of the six patients with a reported remission and a new patient were treated for several months with CoQ_{10} in doses of 390 and 300 mg daily. It was showed that their remaining breast tumors regressed after 3 to 4 months of CoQ_{10} supplementation (76). In another study, 3 breast cancer patients were followed for a total of 3 to 5 years on 390 mg CoQ_{10} daily. One patient had complete remission of liver metastases, another had remission of a tumor that had spread to the chest wall, and the third patient had no microscopic evidence of residual tumor after a mastectomy (75). Because of these patients also received chemotherapy, radiation therapy and surgery additional to CoQ_{10} and the absence of a control group, it is impossible to determine whether any of the beneficial results was directly related to CoQ_{10} therapy. It was shown that ROS increased in malign cells may cause overexpression of antioxidant enzymes and the consumption of CoQ_{10}. Administration of CoQ_{10} by nutrition may induce the protective effect of this substance on breast cancer tissue (77).

CoQ_{10} is essential to aerobic energy production, and increased cell energy may lead to increased antibody synthesis in B lymphocytes (78). Free radical damage to DNA and other cellular molecules may be a factor in cancer development (79). It was shown that CoQ_{10} administration enhances DNA resistance towards H_2O_2-induced oxidation *in vitro* human lymphocytes, but it doesn't inhibit directly DNA strand break formation (80). Oxidative stress and ROS are also involved in the process of apoptosis. The supplementation with the antioxidant formula including CoQ_{10} resulted into a significant decrease in the frequency of apoptotic CD4 and CD8 lymphocytes (81).

Analogs of CoQ_{10} have been demonstrated to inhibit the proliferation of cancer cells *in vitro* and the growth of cancer cells transplanted into rats and mice. They may function as antimetabolites to disrupt normal biochemical reactions required for cell growth and/or survival. Therefore these derivatives may be beneficial as chemotherapeutic agents (70,82).

Diabetes mellitus (DM)

DM is a condition of increased oxidative stress and impaired energy metabolism. Plasma levels of $CoQH_2$ have been found to be lower in diabetic patients than healthy subjects when normalized to plasma cholesterol levels (83). However, 200 mg of CoQ_{10} daily for 6 months did not

improve glycemic control or serum lipid levels in Type-2 diabetics (84). In a trial with Type-1 diabetic patients supplementation with 100 mg of CoQ_{10} daily for 3 months neither increased glycemic control nor decreased insulin requirements (85). Therefore, supplemented CoQ_{10} could be used safely as adjunct therapy for CD in diabetic patients.

It was reported CoQ_{10} may be effective in the neuromuscular symptoms associated with mitochondrial dysfunction in DM (86). Although mitochondrial diabetes accounts for less than 1% of all diabetes, long-term CoQ_{10} addition in doses of 150 mg daily may enhance insulin secretion and prevent progressive hearing loss in these patients (87).

Periodontal Disease

Decreased serum and gingiva levels of CoQ_{10} were recorded in patients with periodontal disease (88,89). In a trial it was found CoQ_{10} 50 mg/day for 21 days to significantly improve clinical aspects of periodontal disease such as inflammation, pocket depth and tooth mobility (90).

Migraine Headaches

CoQ_{10} was shown to prevent migraine. 32 patients with a history of migraine were treated with of CoQ_{10} in doses of 150 mg daily. 61.3% of the patients had a greater than 50% reduction with migraine headache. The reduction in migraine frequency after 1 month of treatment was 13.1% and this increased to 55.3% by the end of 3 months with no side-effects of CoQ_{10} (91).

Male Fertility

An excess of ROS weaken sperm cell function and play a negative role in male fertility. CoQ_{10} may play a positive role in the treatment of asthenozoospermia because of its antioxidant properties. CoQ_{10} levels increased in seminal plasma and in sperm cells after treatment (92). Due to its energy supporting properties, CoQ_{10} is also responsible for sperm production and all energy-dependent processes in the sperm cell. In a research on 17 patients with low fertilization rates were given 60 mg of CoQ_{10} for 103 days. It was demonstrated the sperm's motility rate nearly doubled. Because of the fact that benefits of CoQ_{10} to sperm production and that a related molecule, CoQ_7, may increase the production of healthy sperm, CoQ_{10} was studied in infertile men and it was considered as one part of a pregnancy plan (93,94).

Exposure of to a magnetic field caused a significant reduction in amount, motility and daily production of sperm, and LDH-X activity which was more articulated than that of acute dose. CoQ_{10} was demonstrated to provide protection from magnetic field exposure. Supplemented CoQ_{10} before exposure to high magnetic field caused a important recovery. Treated mice that were

harmed by the effects of the magnetic field recovered more quickly than those that had not been pretreated with CoQ_{10} (95).

Weighting Loss

The resarchers found in a clinical study of 27 obese patients, over 50% of these persons studied were deficient in CoQ_{10}. After 3 months a group given 100 mg of CoQ_{10} daily had lost an average of 38 pounds (96).

Neurodegenerative Diseases

A strong correlation is found between human myotonic dystrophic conditions and deficiencies in mitochondrial functions and energy metabolism, and also a marked biochemical deficiency of CoQ_{10} in the cardiac and skeletal muscles of animals and humans with hereditary muscular dystrophy (97-99). In patients suffering from progressive muscular dystrophy or neurogenic atrophic disease, supplemented CoQ_{10} in doses of 100 mg daily for 3 months was demonstrated improvements in exercise tolerance, leg pain, fatigue, stroke volume, and cardiac output (100).

The CoQ_{10} deficiency appears to initiate problem causing the brain damage, particularly in the cerebellum which is responsible for balance and coordination (101).

It was reported in a patient with an encephalomyopathy, there was a muscle deficiency of CoQ_{10} because both brain and muscle tissues share a common step in the synthesis of this substance (102).

Parkinson's Disease (PD): PD is a degenerative neurological disorder for which no treatment has been shown to slow the progression. There is considerable evidence indicating oxidative damage and mitochondrial dysfunction may play a role in the pathogenesis of PD. Patients with PD have low levels of CoQ_{10} in their mitochondria, which are a major source of free radicals within the cell. CoQ_{10} was shown to be effective in clinical trials of PD because of a key role in supplying energy to chemical reactions in cells and its antioxidant properties. In a clinical study with 80 patients suffering from PD who treated CoQ_{10} only, the disease was progressing less rapidly than would have been expected. CoQ_{10} was safe and well tolerated at dosages of up to 1200 mg daily. In subjects receiving the highest dosage their everyday activities such as feeding, bathing and walking were developed (103,104).

PD is characterized by loss of dopaminergic neurons within the substantia nigra (SN), which is only vulnerable to oxidative damage, having high content of oxidizable dopamine, neuromelanin,

polyunsaturated fatty acids, iron, and relatively low antioxidant complement with high metabolic rate, and related brain stem nuclei, and the presence of Lewy bodies in remaining nerve cells. The genetic factors play a role for the pathogenesis of PD. A point mutation which causes a rare autosomal dominant form of PD was identified in the alpha-synuclein gene on chromosome 4, and a defect of complex I of the MRC was confirmed at the biochemical level. Specificity of this defect was demonstrated for the parkinsonian SN. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin which causes a Parkinson-like syndrome in humans, acts via inhibition of complex I. It was reported in the striatum of patients with PD, a defect in mitochondrial oxidative phosphorylation, in terms of a reduction in the activity of complex I was found in the SN, but not in other areas of the brain, such as globus pallidus or cerebral cortex. Therefore, the specificity of mitochondrial impairment was demonstrated to play a role in the degeneration of nigrostriatal dopaminergic neurons. In addition, MPTP generating 1-methyl-4-phenylpyridine (MPP(+)) destroyed dopaminergic neurons in the SN. CoQ_{10} was able to attenuate the MPTP-induced loss of striatal dopaminergic neurons because of the fact that the serum levels of CoQ_{10} is normal in patients with PD (8,105). It was also showed that the levels of CoQ_{10} and the activities of complex I and complex II/III were significantly correlated (106). CoQ_{10} may play a role in cellular dysfunction in PD and may be a potential neuroprotective agent for parkinsonian patients (107).

It was reported the platelet CoQ_{10} redox state reflected electron transport which influenced deficiency of mitochondrial enzyme activities. Platelet CoQ_{10} redox and the ratio of the reduced form, compared with total platelet CoQ_{10}, were significantly decreased in *de novo* parkinsonian patients (108). On the other hand, there was no relation found between the normality of serum CoQ_{10} and CoQ_{10}/cholesterol ratio with the risk for PD (109).

Huntington's disease (HD): HD is a neurodegenerative disorder characterized by selective degeneration of striatal spiny neurons. Symptoms, such as movement disorders and impaired cognitive function, typically develop in the fourth decade of life and progressively deteriorate over time. Impaired mitochondrial function and glutamate-mediated neurotoxicity was found to play roles in the pathology of HD. Additional CoQ_{10} was demonstrated to decrease brain lesion size in animal models of HD and to decrease brain lactate levels in HD patients (110,111). On the other hand, a combination of CoQ_{10} and remacemide, N-methyl-D-aspartate receptor antagonist, resulted in temporaryly improved motor performance and did not prolong survival in mice with HD (112).

The potential beneficial effects of CoQ_{10} in animal models of PD, amyotrophic lateral sclerosis (ALS) and HD were investigated. CoQ_{10} protected against striatal lesions produced by the mitochondrial toxins malonate and 3-nitropropionic acid which were utilized to model the striatal

pathology occurs in HD and also protected against MPTP toxicity. CoQ_{10} significantly extended survival in a transgenic mouse model of ALS. In addition, it also extended survival, delay motor deficits and weight loss, and attenuate the development of striatal atrophy in a transgenic mouse model of HD. In this model, when combined with the remacemide, CoQ_{10} was able to work synergistically with it (110).

Renal Failure

Chronic renal failure (CRF) is the progressive loss of kidney function. In the early stage, the kidneys no longer function properly but do not yet require dialysis. CoQ_{10} levels were significantly lower ($P < 0.001$) in both hemodialytic and uremic patients compared with the normal group (113). CoQ_{10} was studied in a small pilot study involving 21 subjects with CRF. CoQ_{10} is administered to 11 of the patients while orhers received a placebo capsule. After 4 weeks, the subjects receiving CoQ_{10} had important decreases in serum creatinine and urea while creatinine clearance significantly increased. In addition, the number of patients on dialysis was significantly less in the CoQ_{10} group. 36.2% of the patients in this group were on dialysis while 90.0% of the placebo group were on dialysis at the end of the study. An increase in blood antioxidant levels and a decrease in indicators of oxidative stress were also observed in patients receiving CoQ_{10} (114).

Decreased CoQ_{10} levels were stated several type of diseases. It was also documented that there was decreased level of CoQ_{10} in patients with preeclampsia which is a common disorder of human pregnancy where the normal hemodynamic response to pregnancy is compromised. It was reported during preeclampsia there is a significant decrease in plasma levels of CoQ_{10} compared to normal pregnant women and those who are not pregnant (115).

Formulations and Dosage

Although CoQ_{10} is found in foods such as meat, fish, fish oils and germ of all grains, dietary intake may be inadequate for body's requirements. CoQ_{10} is sold as a nutritional supplement. Its dosage forms include powder-based tablets, powder-filled capsules, softgel capsules, fully-solubilized softgel capsules, chewable wafers, intravenous solution, and intra-oral spray. The highest serum CoQ_{10} concentration is achieved by the fully-solubilized softgel capsule (116).

It is recommend that CoQ_{10} be taken with meals contain fat to improve absorption. 30–60 mg of CoQ_{10} daily (approximately 1 mg/kg of body weight) are typically used to prevent CoQ_{10} deficiency and also, to get normal serum concentrations, 0.7–1.0 μg/mL. Its divided doses are suggested to minimize adverse effects when doses exceed 100 mg/day. In the treatment of chronic heart disease CoQ_{10} is maintained in doses of 100–200 mg/day which may achieve serum

concentrations of 2.0–3.0 μg/mL to have a positive impact on cardiovascular health. In addition to this, therapeutic doses of 90–390 mg/day are used in the treatment of breast cancer (117). In a clinical study, a dose-dependent relationship in the effects of CoQ_{10} treatment for women with high-risk breast cancer was showed. In one patient, during therapy for about one year with 90 mg/day of CoQ_{10}, the tumor "stabilized". 390 mg/day of CoQ_{10} supplementation, the tumor was regressed after one month. After another month, it was reported the tumor was no longer present (76).

Pharmacokinetics

CoQ_{10} is absorbed slowly. Peak plasma levels are reached within 5–10 hours following oral administration. After absorption, which is dependent on the presence of fat in the gastrointestinal tract, CoQ_{10} is sequestered by chylomicrons and then distributed to the liver to be incorporated into very low density lipoproteins. The metabolic end of CoQ_{10} has not been fully explained. The elimination half-life of it is nearly 34 hours; excretion is through the biliary tract and over 60% of the oral dose is recovered in the feces (5).

Adverse Effects

CoQ_{10} is well-tolerated, and no serious adverse effects of CoQ_{10} in humans have been associated with its use and include epigastric discomfort (0.39%), appetite suppression (0.23%), nausea (0.16%) and diarrhea (0.12%) (5). These dose-related complaints are minimized with dose reduction and/or dose division as mentioned above. Higher than 300 mg daily was reported to increase serum LDH and SGOT levels, but no hepatotoxicity was observed. Late night administration was stated to cause insomnia (117).

It a trial with 2664 patients minor adverse effects was reported in 1.5% of the patients. The daily dosage of CoQ_{10} was 50-150 mg orally. After test treatment of 3 months, improved clinical signs and symptoms as follows: sweating 79.8%, oedema 78.6%, cyanosis 78.1%, pulmonary rales 77.8%, palpitations 75.4%, vertigo 73.1%, jugular reflux 71.81%, subjective arrhythmia 63.4%, insomnia 62.8%, nocturia 53.6%, dyspnoea 52.7%, and enlargement of liver area 49.3% (37).

Drug Interactions

It was reported that HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors, also known as statins widely used cholesterol-lowering medications which block the synthesis of mevalonic acid, a precursor to CoQ_{10}, decrease endogenous CoQ_{10} levels (118,119). Oral hypoglycemics (glyburide, acetohexamide, tolazamide) and beta-blockers and inhibit enzymes that produce CoQ_{10} and decrease endogenous CoQ_{10} levels (117,120). Based on the structural

similarity of CoQ_{10} to vitamin K, CoQ_{10} supplements was reported to decrease the anticoagulant activity of warfarin decreases (121).

CONCLUSION

CoQ_{10} is a considerable member of the electron transport chain which is required for mitochondrial ATP synthesis and also an important antioxidant effective within mitochondria. Supplemented CoQ_{10} has concluded with metabolic and clinical improvement, and demonstrated that it may be useful as adjunctive therapy additional to conventional treatments. The main idea running through our examination has been CoQ_{10}'s principal role of on liveliness.

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