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Review Article

Coenzyme Q_{10} therapy in current clinical practice

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ABSTRACT

Coenzyme Q_{10} (CoQ_{10}) is a naturally occurring, lipid soluble, essential compound and is also known as ubiquinone. CoQ_{10} acts as an intermediate of the electron transport chain situated in membrane of mitochondria and vital for ATP production and cellular respiration. CoQ_{10} also serves as an intercellular antioxidant. All the clinical use of CoQ_{10} are based upon these two functions. CoQ_{10} levels are altered in a number of oncological as well as non-oncological diseases. Furthermore, recent data indicate that CoQ_{10} has an impact on the expression of many genes involved in metabolism, cellular transport, transcription control, and cell signaling, making CoQ_{10} a potent gene regulator. CoQ_{10} supplementation is useful in diseases associated with CoQ_{10} deficiency which includes primary and secondary CoQ_{10} deficiencies, fibromyalgia, diabetes mellitus, mitochondrial diseases, neurodegenerative diseases, cardiovascular disease, cancer, male infertility and periodontal disease. Clinical presentations of severe CoQ_{10} deficiency include severe infantile multisystemic disease, encephalomyopathy, isolated myopathy cerebellar ataxia and Leigh syndrome with growth retardation. Oral CoQ_{10} administration can correct CoQ_{10} deficiency since it increases CoQ_{10} tissue levels. CoQ_{10} therapy has no serious side effects in humans and new formulations have been developed that increase CoQ_{10} absorption and tissue distribution. Future trends involving CoQ_{10} in many diseases needs more clinical trials for better understanding of CoQ_{10} efficacy.

Keywords: $CoQ_{10,}$ Oxidation, Antioxidant, Cancer

INTRODUCTION

Coenzyme Q_{10} (CoQ_{10}) is a naturally occurring essential compound found in virtually every cell of the human body. CoQ_{10} is also known as ubiquinone because of its quinone structure and ubiquitous presence in nature.[1] It is a lipid soluble substance which is found in cell membranes and is well known for its primary role as an intermediate of the electron transport chain localized in mitochondrial membranes and is vital for aerobic cellular respiration.[2] Adequate amounts of CoQ_{10} are essential for ATP production and cellular respiration. CoQ_{10} also acts as an intercellular antioxidant and is present in blood, cell membranes low density lipoproteins and high density lipoproteins.[1] CoQ_{10} protects proteins, DNA and membrane lipids.[3] CoQ_{10} is structurally similar to vitamin K, but still it is not considered a vitamin because it is the synthesized *de novo* in the body.[1] The first aromatic precursor in the CoQ_{10} biosynthesis is para-hydroxybenzoic acid from the amino acid tyrosine and constitutes its quinoid ring structure. The tail is consist of 10 isoprenoid units which is derived from the mevalonate pathway.[1]

Endogenous CoQ_{10} levels are determined by both the rate of production and the rate of consumption in the body and is regulated by a number of physiological factors.[1] These levels are altered in a number of disease states including cancers, along with cardiovascular disease and degenerative muscle disorders and many others.[1,4] CoQ_{10}

acts as a potent gene regulator and significantly affect the expression of genes mainly involved in intermediary metabolism, cell signaling, inflammation, cellular transport and transcription control. However, the molecular mechanisms by which CoQ_{10} is inducing these pleiotropic effects has yet not completely understood.[1,4] CoQ_{10} supplementation can treat CoQ_{10} deficiency states including primary and secondary CoQ_{10} deficiencies, fibromyalgia, cardiovascular disease, male infertility, diabetes mellitus, cancer, mitochondrial diseases, neurodegenerative diseases and periodontal disease.[1] CoQ_{10} levels decrease with advancing age which may contribute to some manifestations of aging. CoQ_{10} deficiency could result from a genetic or acquired defect in CoQ_{10} synthesis or utilization, impaired CoQ_{10} synthesis due to nutritional deficiencies such as vitamin B6 deficiency, a cofactor essential for CoQ_{10} biosynthesis and increased tissue needs. Severe CoQ_{10} deficiency may lead to cerebellar ataxia, severe infantile multisystemic disease, encephalomyopathy, Leigh syndrome with growth retardation and isolated myopathy. Orally administered CoQ_{10} can increase tissue levels of the nutrient which makes possible to correct CoQ_{10} deficiencies.[1]

Cancer is a burning issue in current clinical practice.[5] CoQ_{10} is a key molecule in all energy requiring processes, including immune function, angiogenesis, proliferation, and apoptosis, suggesting the potential of CoQ_{10} for initiation and progression of cancer.[6]

Despite the critical role of CoQ_{10} in many cellular functions and gene expression, its potential relationship with many of the diseases and cancer development and progression has not received appropriate attention. Epidemiological or clinical studies of plasma or tissue CoQ_{10} involve limited numbers of subjects and are rare in the literature.[1,4,6] This review intends to critically analyze the role of CoQ_{10} (if any) in current clinical medical practice.

MECHANISM OF ACTION

Table 1 shows the mechanism of action at biochemical level,[2] molecular level[1] and level at drug induced apoptosis.[7] As superoxide generation occurs secondarily for drug-induced apoptosis, free radical generation is not necessary to exert cytotoxic effect on tumor cells.[7] However, the molecular mechanisms through which CoQ_{10} induces these pleiotropic effects has yet completely not understood.[1] Thus, CoQ_{10} acts within cells to produce energy for cell growth and maintenance.[2]

ABSORPTION, TISSUE UPTAKE AND PHARMACOKINETICS

Table 2 shows the different parameters related to CoQ_{10} absorption and pharmacokinetics. Absorption of CoQ_{10} is slow from the small intestine, because CoQ_{10} has a high molecular weight and is not water soluble. CoQ_{10} then passes into the lymphatics, blood and finally to tissues. Higher plasma CoQ_{10} levels are necessary to facilitate peripheral tissues uptake. Further trials are needed to elucidate whether diet, age, gender, dosage formulation, lipoprotein status, or other factors may affect CoQ_{10} bioavailability. Monitoring of plasma CoQ_{10} concentrations is useful after 3-4 weeks of constant dosing, when steady-state plasma concentration exist, with dosage levels from 5-10 µg/ml.[1]

CoQ_{10} levels in cells and tissues decrease with age, and cellular levels below a critical limit are incompatible with life. In contrast, some studies suggest that plasma CoQ_{10} levels rise with age, and are higher in postmenopausal women. Supplemental CoQ_{10} increases circulating α-T levels in humans, however, the physiological regulation of circulating CoQ_{10} is unknown.[6]

Table 1: Different levels of mechanism of action of CoQ_{10}[1,2,7]

Level	Action
Biochemical level	Having a direct regulatory role on succinyl and the reduced form of nicotinamide adenine dinucleotide dehydrogenases (NADH)
	Acting as a catalyst and playing an integral role in regulating the cytochrome bc1 complex
	Having direct membrane-stabilizing properties that are separate from its role in oxidative phosphorylation
Molecular level	Effect on genes involved in cell signalling
	Effect on genes involved in transport and transcription control
	Effect on genes involved in intermediary metabolism
	Effect on genes involved in inflammation
Drug induced apoptosis	Release of cytochrome c from mitochondria
	With the concomitant formation of superoxide radicals, hydrogen peroxide and highly toxic hydroxyl radicals via Fenton and Haber-Weiss reactions

Table 2: Different parameters related to CoQ_{10} absorption and pharmacokinetics[1,10,11]

CoQ_{10} parameter	Remarks
Normal range	0.40-1.91µmol/L (0.34-1.65 µg/ml) Males have higher levels than females Younger have higher level than adults
Sources	Naturally in diet Heart, chicken leg, herring, trout
Daily intake from food	3-5 mg/day
Absorption	3 times faster with food intake Slightly better with oil based forms of CoQ_{10}
Therapeutic dosage: Adults Children	 Upto 1200 mg/day Upto 10 mg/kg/day
Peak plasma level	Achieved 5-10 hour after ingestion

SIDE EFFECTS AND DRUG INTERACTIONS

CoQ_{10} treatment is safe, even at very high doses. Most of the studies have not reported significant side effects of CoQ_{10} therapy leading to halt it. Most common side effects are on gastrointestinal system such as anorexia, nausea, vomiting, abdominal discomfort and diarrhoea. Headache and allergic rash are also seen.[1] Other side effects of CoQ_{10} may include heartburn, elevated liver enzymes, insomnia, dizziness, irritability, headache and photophobia; however, regardless of the dosage used, few untoward effects have been observed.[2] CoQ_{10} may increase the risk of bleeding due to its antiplatelet effect. It undergoes biotransformation in the liver and is eliminated via the biliary tract, so it gets accumulated in patients with biliary obstruction or hepatic impairment.[1] Table 3 shows the various pharmacologic interactions of CoQ_{10}.[1]

Table 3: Various pharmacologic interactions of CoQ_{10}.[1]

Agent	Interaction
Beta blockers (Propranolol, metoprolol)	Inhibit CoQ_{10} dependent enzymes
Phenothiazines, tricyclic antidepressants	Inhibit CoQ_{10} dependent enzymes
Antihypertensive drugs	Additive antihypertensive effect
Warfarin	Counteract its anticoagulant effect by acting like vitamin K
Cholesterol-lowering drugs (Lovastatin and pravastatin)	Inhibit the enzyme HMG-CoA reductase, required for synthesis of cholesterol as well as CoQ_{10}, resulting in a decreased serum CoQ_{10}
Insulin	CoQ10 may improve beta-cell function and enhance insulin sensitivity, which may reduce insulin requirements for diabetic patients.

USES

CoQ_{10} is used in many oncological as well as non-oncological diseases. Table 4 shows the various uses of CoQ_{10}.

CoQ_{10} IN ONCOLOGY

CoQ_{10} via redox signaling controls both energy metabolism and regulation of cell death, so it is a vital pathway in cancer research.[5] Free radicals have been implicated in the action of many chemotherapeutic drugs. Camptothecin and other chemotherapeutic agents, such as doxorubicin, etoposide, and methotrexate, induce an increase in reduced CoQ_{10} levels as part of the antioxidant defense against free radical production under these anticancer treatments in cancer cell lines. Furthermore, CoQ_{10} biosynthesis inhibition blocked camptothecin-induced CoQ_{10} increase, and enhanced camptothecin cytotoxicity. CoQ_{10} increase is implicated in the cellular defense under chemotherapy treatment and may contribute to cell survival.[8]

Literature suggested that at least 80% of cancer patients who are undergoing multimodality treatment, experience a significant degree of fatigue that may negatively impact their treatment tolerance, emotional well-being and quality of life (QOL).[2] Many clinical trials have addressed correlation between CoQ_{10} and fatigue.

Table 4: Various uses of Coenzyme Q_{10}.[1,10]

Conditions	Conditions
Dietary supplement	**Used in CoQ_{10} deficiency states**
Fatigue	Primary CoQ_{10} deficiencies
Cardiovascular conditions	Secondary CoQ_{10} deficiencies such as mitochondrial diseases
Atherosclerosis	Advancing age
Congestive heart failure	Encephalomyopathy
Hypertrophic cardiomyopathy	Severe infantile multisystemic disease
Cardiac fatigue	Leigh syndrome with growth retardation
Neurodegenerative conditions	Isolated myopathy
Early stage Parkinson's disease	Fibromyalgia
Inherited defects in CoQ_{10} biosynthesis	Cardiovascular disease
Cancer	Neurodegenerative diseases
Prevent cardiotoxicity in patients receiving anthracycline based chemotherapy	Cancer
Breast cancer	Diabetes mellitus
Lung cancer	Male infertility
Prostate cancer	Periodontal disease
Melanoma	Down's syndrome
Liver cancer	Migraine
Cancer cervix	Pregnancy (Preeclampsia)

Breast cancer

Plasma CoQ_{10} levels are significantly associated with risk of breast cancer, in women diagnosed at least one year after blood draw, suggesting that breast cancer CoQ_{10} association is somewhat attenuated with the inclusion of women with latent breast cancer.[9] Increased breast cancer risk is seen with women at either extreme of CoQ_{10}. Lowest risk for breast cancer development is seen with CoQ_{10} levels of 500-800 ng/ml. Significantly increased risk for breast cancer is seen with CoQ_{10} levels >1000 ng/ml.[6] Some authors reported lower plasma CoQ_{10} levels in breast cancer patients.[10,11] Folkers et al. reported that CoQ_{10} deficiency is seen in 23% of breast cancer patients as compared to 4% of cancer free women.[10] Serum CoQ_{10} levels are reported higher in postmenopausal women as compared to premenopausal women, which suggests that

circulating gonadotrophin or steroid hormone concentrations may affect plasma CoQ_{10} levels.[12] In postmenopausal breast cancer patients, there is an inverse association of CoQ_{10} with SHBG, so higher SHBG concentrations are associated with reduced risk of breast cancer.[9] Chai et al[9] found that higher plasma CoQ_{10} levels are seen with current HRT (hormone replacement therapy) users as compared to non-users. CoQ_{10} is positively associated with high risk of breast cancer in individuals with low γ-tocopherol levels, but it needs further investigational trial.[9,13] To conclude the potential role of CoQ_{10} in breast cancer etiology, prospective studies are needed with a longer follow up and larger sample size.[9]

Doxorubicin (Adriamycin) is a part of standard adjuvant therapy for breast cancer, and 3-20% of the patients develop cardiotoxicity.[7] During doxorubicin treatment, in skeletal muscle and cardiac muscle, an acute rise is followed by a marked post-treatment decrease in the levels of CoQ_{10}. Plasma CoQ_{10} levels are raised by 300-400% with 300 mg of CoQ_{10} per day for 11 days. Doxorubicin-induced cardiotoxicity can be prevented by CoQ_{10} administration either before or during doxorubicin administration, as CoQ_{10} slows down or prevents the displacement of CoQ_{10} by doxorubicin metabolites. Increased doses of doxorubicin can be administered with CoQ_{10} administration.[7,14] Tamoxifen (TAM) is used in adjuvant therapy for all stages of breast carcinomas and in chemoprevention of high-risk group. Co-administrating CoRN (CoQ_{10}, riboflavin and niacin) with TAM has shown favorable impact on various blood chemistry profiles[15] by reducing the serum tumor marker levels of CEA and CA 15-3, thereby offering better cancer prognosis by reducing the risk of developing cancer recurrence and metastasis, improved quality of life.[15,16] Tamoxifen therapy is found to cause hypertriglyceridemia and thereby increasing the risk of cardiovascular disease. Co-administration of CoQ_{10} (100 mg/d) along with tamoxifen (10 mg, twice a day) to breast cancer patients reduced the level of angiogenesis markers and lipid levels.[17]

Prostate cancer

Some authors found no effect of CoQ_{10} on hormonal levels or PSA levels in prostate cancer patients and suggested further studies to assess protective effect of higher levels of circulating CoQ_{10}.[18,19] CoQ_{10} acts as modulator of differential gene expression and helps in free radical production in prostate cells. CoQ_{10} supplementation significantly lowered cell growth of the PC3 cancer line of prostate cancer.[20]

Cervical cancer

Mean plasma levels of CoQ_{10}, alpha-tocopherol and gamma-tocopherol were significantly lower, in patients with various grades of cervical intraepithelial neoplasia CIN and cervical cancer. An inverse association is seen between both plasma CoQ_{10} and alpha-tocopherol concentrations and histological grades of epithelial lesions. The low plasma concentrations of CoQ_{10} may be due to decreased endogenous CoQ_{10} biosynthesis or deficient dietary intake.[21]

Melanoma

Rusciani et al. reported significant decreased rates of recurrence and negligible adverse effects with recombinant interferon alpha-2b and CoQ_{10} as a postsurgical adjuvant therapy for stage I and II melanoma.[22] CoQ_{10} levels were significantly lower in patients who developed metastases than in the metastasis-free subgroup and concluded that baseline plasma CoQ_{10} levels are independent and powerful prognostic factor that are used to estimate the risk for melanoma progression.[23]

Lung cancer

Significantly lower erythrocyte CoQ_{10} levels were seen in patients with lung cancer and it may be a useful parameter for lung cancer risk assessment.[24]

Liver cancer

Tharappel et al found that dietary antioxidants were not effective at inhibiting hepatic tumor promotion by PCBs [3,3',4,4'-Tetrachlorobiphenyl (PCB-77)].[25]

Other cancers

Hertz et al. administered supplements of CoQ_{10}, vitamin C, selenium, folic acid and β-carotene, to patients with end-stage cancer and evaluated the survival of these patients. Primary cancers were located in the brain, oesophagus, breast, stomach, lungs, colon, pancreas, kidneys, ovaries, prostate and skin. Median actual survival was 17 months, which is more than 40% longer than the median predicted survival. Out of all, 24% survived for less time than predicted, whereas 76% survived for longer. Treatments were tolerated very well with little side effects.[26] Sieswerda et al. showed that CoQ_{10} may be used for treating anthracycline induced cardiotoxicity during and after treatment for childhood cancer.[27] Forgionne et al. in their study on bovine cartilage, CoQ_{10}, and wheat grass therapy for primary peritoneal cancer, reported encouraging results with regards to objective and subjective measures.[28]

NON-ONCOLOGICAL ROLE OF CoQ_{10}

Physical capacity

Individuals performing high physical activity show relatively lower blood levels of CoQ_{10}.[4] There is a positive association between serum levels of CoQ_{10} and maximal oxygen uptake, CoQ_{10} supplementation has a positive effect on physical capacity. Out of all studies;

some indicated a positive effect, some indicated no effect and very few indicated a negative effect of CoQ_{10} on physical capacity.[4] An increase in creatine kinase levels due to increased cell damage is seen in the blood after intake of a CoQ_{10} supplement.[29] The experimental studies so far have not clarified the importance of Q_{10} in physical capacity.[4]

Atherosclerosis

CoQ_{10} in its reduced form, ubiquinol, inhibits protein and DNA oxidation. Ubiquinol as such inhibits the peroxidation of lipids of the cell membrane and lipoproteins present in the circulation.[1] CoQ_{10} supplementation results in increased resistance of low-density lipoproteins to the initiation of peroxidation of lipids.[1,30] Moreover, direct anti-atherogenic effect of CoQ_{10} has also been seen. CoQ_{10} supplementation at a dose of 150 mg/day can decrease the inflammatory marker IL-6, decrease oxidative stress and increase antioxidant enzyme activity in patients with atherosclerosis.[1]

Dyslipidemia and statin drugs

Dyslipidemia associated with elevated cholesterol level is treated with 3-HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors also known as statins.[1] Because both CoQ_{10} synthesis and cholesterol depend on HMG-CoA reductase, so both can be blocked with statins. Depletion in CoQ_{10} secondary to statin therapy may account for the statin-induced myopathies, the most serious of which is rhabdomyolysis.[1,31] Consequently, CoQ_{10} supplementation is highly recommended to prevent statin associated myopathies. However, clinical evidence is limited and controversial for this use.[1]

Cardiovascular disease

Oxidative stress plays a major role in the pathogenesis of cardiovascular diseases including hypertension and heart failure. Heart failure is characterized by a loss of myocardial muscle contractility due to energy depletion in the mitochondria which is associated with low endogenous levels of CoQ_{10}. Myocardial deficiency of CoQ_{10} is reported in endomyocardial biopsy from patients suffering from cardiomyopathy, and CoQ_{10} deficiency correlated well with the severity of disease, suggesting that CoQ_{10} therapy may improve the quality of life.[1] The level of blood and myocardial CoQ_{10} was negatively associated with the severity of symptoms and the degree of left ventricular dysfunction. CoQ_{10} supplementation benefits by improving cardiovascular function via increased energy production, improved cardiac muscle contractility, and its potent antioxidant activity, particularly the prevention of oxidation of low-density lipoproteins.[4] Signs of improvement in clinical parameters, haemodynamic parameters and/or exercise capacity were registered when conventional treatment was accompanied by CoQ_{10} supplementation. CoQ_{10} supplementation reduced development of angina pectoris, arrhythmias and ventricular dysfunction in patients with acute myocardial infarction.[4,32] CoQ_{10} increases the patients' stamina during exercise on a treadmill, delaying the development ST depression as a sign of oxygen deficiency in the myocardium, and delaying the onset of angina pectoris. Several studies found that fewer angina pectoris attacks were provoked and that daily use of nitroglycerine was reduced. However, larger, long-term studies are necessary to confirm these observations.[4]

Hypertension

CoQ_{10} supplementation decreases systolic as well as diastolic blood pressure.[4] Supplementation with CoQ_{10} might decrease the need to take multiple antihypertensive agents. It decreases peripheral resistance by nitric oxide preservation.[33] Superoxide radicals are overproduced in some forms of hypertension, which inactivate nitric oxide and CoQ_{10} may prevent it.[1]

CoQ_{10} may also boost the production of the prostacyclin which is a prostaglandin, inhibitor of platelet aggregation and a potent vasodilator, and/or CoQ_{10} may increase the sensitivity of arterial smooth muscles to prostacyclin. Further investigations are clearly necessary before CoQ_{10}'s potential in the treatment of high blood pressure is fully explored.[1]

Cardiac and vascular surgery

Several experiments have described the effect of CoQ_{10} supplement on different clinical, haemodynamical and biochemical parameters in connection with cardiac surgery for ischemic heart disease or valvular heart disease.[4] In one study of patients with peripheral vascular disease, Chello et al. found less enzyme leakage (Creatine kinase and lactatedehydrogenase) and lower levels of split products of the oxidative burst in CoQ_{10} pre-treated patients.[34]

Diabetes

Oxidative stress plays a key role in the pathogenesis of diabetes. In type 2 diabetic patients, serum CoQ_{10} levels are decreased and may be associated with subclinical diabetic cardiomyopathy.[1] CoQ_{10} supplementation with 200 mg daily for 12 weeks raised plasma levels of CoQ_{10}, improved endothelial function of the brachial artery, significantly decreased both diastolic and systolic blood pressure, decreased HbA_{1C} (glycosylated hemoglobin), and, significantly improved both endothelial and non-endothelial vasodilation of forearm via combining with fenofibrate. Furthermore, it is reported that if ubiquinone is given for 12-week period, it improves nerve conduction parameters and clinical outcomes of diabetic neuropathy. CoQ_{10} decreases oxidative stress without significant side effects.[35]

NEUROLOGICAL CONDITIONS

Parkinson's disease

CoQ_{10} protect the nigrostriatal dopaminergic system and have neuroprotective effects in patients with early and mid-stage Parkinson's Disease (PD).[1] CoQ_{10} play a major role in the cellular dysfunction of PD. Significantly decreased CoQ_{10} levels are observed in mitochondria of blood and platelets, and is also seen in plasma of PD patients.[36]

Huntington's disease

Huntington's Disease (HD) is caused by early oxidative damage and mitochondrial dysfunction due to expanded polyglutamine sequence, leading to an energy deficit.[1] High dose CoQ_{10} is safe and tolerable and can reduce reactive oxygen species and may ameliorate the neurodegenerative process in HD patients.[37]

Alzheimer's disease

As CoQ_{10} protects oxidative damage and attenuates mitochondrial dysfunction, so CoQ_{10} is neuroprotective in Alzheimer's disease. However, in some trial, biomarkers related to amyloid or tau pathology, in cerebrospinal fluid, were not influenced by CoQ_{10} supplementation.[1]

MITOCHONDRIAL DISORDERS

CoQ_{10} is often decreased in muscle tissue of patients with mitochondrial myopathy, and CoQ_{10} is commonly used for the treatment of primary mitochondrial disorders in dosages of 30 to 300 mg/day.[1] Researchers reported a trend towards decreased serum pyruvate and lactate levels, less fatigue during daily duties, and improved muscle endurance.[1]

Friedreich's ataxia (FRDA)

The oxidative damage, mitochondrial respiratory chain dysfunction, and iron accumulation play valuable roles in the mechanism of FRDA. For treating FRDA, avenues targeting antioxidant protection and enhancement of mitochondrial oxidative phosphorylation may play a role.[1] On administring CoQ_{10} and vitamin E, a significant improvement in energy synthesis of mitochondria is seen that is associated with improved cardiac function and a decline in disease progression.[38]

Fibromyalgia

Oxidative stress is associated to clinical symptoms in Fibromyalgia (FM). Reduced CoQ_{10} levels, increased levels of mitochondrial superoxide, decreased mitochondrial membrane potential, and increased levels of lipid peroxidation in blood mononuclear cells are seen in FM patients.[1,39] CoQ_{10} supplementation in FM patients showed a significant reduction of symptoms.[39]

TREATMENT OF CoQ_{10} DEFICIENCIES

CoQ_{10} deficiency is a treatable condition. Patients with CoQ_{10} deficiency show clinical improvement with oral supplementation of CoQ_{10}. Only partial amelioration is seen in cerebral symptoms because of irreversible damage to brain structure before treatment and because of poor penetration of CoQ_{10} across the blood-brain barrier.[1] CoQ_{10} deficiency is involved in degenerative neuronal and muscle diseases and cardiomyopathies. The major phenotypes provoked by CoQ_{10} deficiencies are ataxia, encephalomyopathy, nephrotic syndrome, severe infantile multisystemic disease, Leigh syndrome with growth retardation, cerebellar ataxia, and isolated myopathy.[40] The cerebellum is the first tissue to get affected from a pathological deficiency of CoQ_{10} because cerebellum has the narrowest safety margin. CoQ_{10} deficiencies are due to autosomal recessive mutations and are classified as primary CoQ_{10} deficiencies when these mutations affect genes of CoQ_{10} biosynthesis pathway or secondary CoQ_{10} deficiencies if the cause is other than the genetic defects.[1] In a study, patients with renal failure and encephalomyopathy received oral CoQ_{10} at doses of 5 mg/kg/day or 30 mg/kg/day; patient with myopathy received 500 mg/day, and patient with cerebellar ataxia received 2,500 mg/day of CoQ_{10}. The doses were reduced at an interval of every 3 months. These cases showed a good response to CoQ_{10} supplementation.[1] Myopathic CoQ_{10} deficiency also responded significantly to CoQ_{10} supplementation, and after treatment of 8 months, mitochondrial enzymes increased, CoQ_{10} level normalized, excessive lipid storage resolved, and the proportion of apoptotic fibers decreased from 30 to 10%.[41]

MALE INFERTILITY

Both the antioxidant and bioenergetic role of CoQ_{10} suggest a possible involvement in male infertility and sperm biochemistry.[4] CoQ_{10} concentration in seminal fluid correlates with sperm count and motility. CoQ_{10} distribution between seminal plasma and sperm cells got altered in patients with varicocele who presented with higher oxidative stress and lower antioxidant capacity.[1] In seminal fluid, an inverse correlation is seen between hydroperoxide levels and ubiquinol/ubiquinone ratio, and also between this ratio and percentage of abnormal sperm forms. CoQ_{10} supplementation led to an increase in CoQ_{10} concentration, both in sperm cells and seminal plasma, and improvement in sperm motility among infertile patients suffering from idiopathic asthenozoospermia. CoQ_{10} improves the semen quality and also the pregnancy rate.[1,4]

PERIODONTAL DISEASE

Levels of CoQ_{10} in the gingiva declines with age, and frequency of periodontal disease increases with age.[4] Periodontal pathogens can induce Reactive Oxygen Species (ROS) overproduction and, so, it may cause periodontal cell and collagen breakdown. Ubiquinol serves as an endogenous antioxidant which increases

CoQ_{10} concentration of CoQ_{10} in the diseased gingiva and ROS are scavenged, reduction of collagen degradation and effectively suppresses advanced periodontal inflammation.[1]

MIGRAINE

Impaired energy metabolism in brain may cause migraine. CoQ_{10} deficiency is common in pediatric and adolescent migraine.[1] Rozen et al reported 50% reduction in the frequency of migraine headaches when supplemented with 150 mg CoQ_{10} daily for 3 months.[42]

PREGNANCY

Plasma levels of CoQ_{10} increase with each trimester of pregnancy and fetal wasting with subsequent spontaneous abortion has been correlated with low CoQ_{10} levels. CoQ_{10} supplementation decreases the risk of development of pre-eclampsia.[1,43]

DOWN'S SYNDROME

Oxidative stress play a key role in Down's syndrome (DS) pathology, suggesting that oxidative imbalance contributes to the clinical manifestation of DS. The effect of CoQ_{10} treatment in DS reflects its antioxidant efficacy and modulates DNA repair mechanisms.[44]

AGING

CoQ_{10} levels decrease with age and it may lead to the development of chronic diseases in old people. CoQ_{10} is involved in various cellular processes, so maintenance of CoQ_{10} functional levels at cell membranes can be a key strategy to enhance health during aging.[1]

CONCLUSION

CoQ_{10} is used in a number of cancers including cancers of breast, cervix, prostate, melanoma and various others. CoQ_{10} is also useful in various other diseases like cardiovascular diseases, neurodegenerative diseases, mitochondrial deficiency disorders etc. Future research needs to address many unanswered questions regarding the effect of orally administered CoQ_{10} on the various diseases in terms of improvement in local and/or systemic control and the studies need to include more number of patients to interpret a concrete result. There is a need to understand the impact of oxidative stress on the therapeutic efficacy of cancer chemotherapy, the role that oxidative stress plays in the development of chemotherapy-induced side effects and the effect of antioxidants on anticancer activity and the development of therapy-induced adverse effects. Fundamental studies that elucidate the impact of oxidative stress, and specifically ROS-generated aldehydes, on cell cycle progression and apoptotic pathways may guide us to interventions that could enhance chemotherapeutic efficacy. Finally, clinical studies must be conducted including large number of patients to determine both the short-term and long-term impact of antioxidants, alone and in combination, upon the various above-said diseases and upon the efficacy of cancer chemotherapy and the development of chemotherapy-induced side effects.

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