The Role of Co-Enzyme Q10 in The Respiratory Chain and Some of Its Clinical Indications: A review

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ABSTRACT

Background: The usage of supplements becomes an important part of everyone health since many of these materials have produced real improvement in general health. These materials are not approved by organization like Food and Drug Administration in the US and the Food Safety Authority in Europe as drugs but their usage as supplement are approved globally. The supplements that will discuss in this review is co-enzyme Q10. It is a potent antioxidant and an essential part of respiratory chain. It acts as a mobile electron carrier between respiratory complexes. When co-enzyme Q10 transfer electron in the oxidative system, it acts to transport proton out of the mitochondria and this produce concentration gradient across membrane. Proton returns inside by enzymatic machine which involved ATP synthesis. Co-enzyme Q10 is the third wide-world used supplement. There are many studies confirm it benefit in many clinical conditions. These include the cardiovascular system, protection against statin induce myopathy, diabetes, neurodegenerative disease in addition to improvement in liver functions. These benefits occurred mainly due to its antioxidant effect and electron scavenging ability which result in reducing oxidative stress and related cell and tissue damage.

Objective This study tries to show the important role of coenzyme Q10 in energy production and spots the light toward the main clinical application of this supplement. Coenzyme Q10 is one of the main elements in the respiratory chain and it is endogenously synthesis since its presence is essential for life. Its availability may reduce in many disease conditions so supplementation of it within diet may become important in management of various disorders.

Keywords: Co-enzyme Q10, supplements, respiratory chain, mitochondrial bioenergetics, oxidative stress, protective effect.
signification of supplements

It is the unprecedented challenges that sustaining the health of more than nine billion people by 2050. Researches in the nutrition and food areas are required to get solutions to these challenges which affect food systems and health. Indeed, one of the top of priorities for (WHO) World Health Organization is nutrition and food security. The enhancements in health as a result of increase health care in the last years have contributed to an improve in the life average, and this result in a remarkable increase of elderly worldwide (1).

When population getting old, this led to a harsh increase of the prevalence of non-infectious and chronic diseases. Cardiovascular diseases, such as hypertension, atherosclerosis, strokes had become the leading causes of death worldwide in the past decade, other non-infectious diseases including diabetes mellitus, cancer, dementias such as Alzheimer disease and others are in the list of the main 10 leading cause of death globally (1).

In truth, those are not only the main leading causes of death that produce killing in people more than all other causes combined, but they are also replacing malnutrition and communicable diseases as a cause of disability or early death. Although non-infectious diseases have become epidemic in their magnitudes, they can be prevented, in addition they could be reduced to significant extant by early detection, minimizing of their risk factors, and suitable management. In this spirit, governments are working to support lifestyles in healthy manner, and this to improve morbidity and mortality issues, and also to reduce the costs of health care (2).

Furthermore, knowledge about health, including applications related to food and fitness, make persons more alert about their own health’s (3). Clients are now being more alert than any other time about the constituents in foods and the characteristic properties of these constituents, and by the increase number of clients who consider food as medication, food supplementation be obvious as one of the most rapid developing health related goods (4).

These in general have positive inferences in wellbeing condition, still, health related costs and the consuming growth are necessitating a critical need for physicians, specialized dietitians, and other regulators to get systematic data on safety and efficacy of a wide range of active constituents occurred in food supplements. Many clients think that supplements are natural occurring healthy foodstuffs with no possible interactions with drugs or
Co-enzyme Q10 is an important element of cell mechanism used for generate ATP which acts to provide energy for almost all cellular functions. Co-enzyme Q10 exists in three redox states and this nature is essential for its function (12):

- Fully oxidized ubiquinone (CoQ10)
- Fully reduced ubiquinol (CoQ10H2)
- Radical semiquinone intermediate (CoQ10H)

The production of ATP is occurred in the inner mitochondrial membrane, where a higher concentration of co-enzyme Q10 can be detected. The coenzyme Q10 has a distinctive role since it can not only transfer electrons from primary substrates to oxidative system but can, in the same time, transfer protons to the out of the mitochondrial. By this transfer, proton gradient across the mitochondrial membrane can generate and when the protons return to inside mitochondria by the enzymatic machine for ATP synthesis, they act as a method to ATP formation. The coenzyme Q10 binds to the oriented enzymatic complexes. It acts to oxidize and release protons to the outside of mitochondria and picks up protons and electrons on the inside part of the mitochondrial membrane (12, 13).

There are five types of protein complexes in the mitochondrial membrane, two of them involved in protons and electrons transferred through coenzyme Q10. The first is known as the primary reductase where co-enzyme Q10 is reduced by the action of NADH this also known as (complex I). The reduction process involved four protons transport across membrane for every co-enzyme Q10 reduced (12, 13)

The exact details about electron transport in (complex I) are still not fully understood, still, it has suggested that
coenzyme Q10 is reduced and then re-oxidized in (complex I) two times after that, electrons transferring to another lightly bound co-enzyme Q10 to produce ubiquinol which travels across the lipid of mitochondrial membrane to the another complex where ubiquinol oxidation occurred again in (complex III) and this happens with the transfer of protons against it concentration gradient across membrane (12, 13).

Unlike the details about protons transport in complex I, the details about ubiquinol oxidation and binding at the binding site of complex III are well known. Equal to complex I, there is oxidation, reduction and re-oxidation, also with the oxidation there is a proton release step to the outside so that protons released occurred in the right direction. Again oxidation-reduction cycle permits four protons to pass the membrane for each ubiquinol oxidation cycle (12).

In a normal forward electron transfer chain, co-enzyme Q10 accepts electrons from both complexes I and II and transport them to complex III. In complex III, the Q cycle happened, with impelling of protons from the matrix to the intermembrane space. The complex III contains two distinct binding sites of co-enzyme Q10. Reduced ubiquinol (UQH$_2$) bind at the O site (Qo site), transporting one electron to cytochrome c (cyt c) and the other electron pass down to the I site (Qi site), where the electron attaches to co-enzyme Q10 (ubiquinone), forming ubisemiquinone intermediate (UQH$_2^+$), or attach to (UQH$^+$) generated ubiquinol (UQH$_2$). The formation of oxidized co-enzyme Q10 occurred at the (Qo site), while reduced ubiquinol (UQH$_2$) formed at the (Qi site). When electrons transport is occurred, they may leak out and attach to oxygen, forming superoxide anion (O$_{2}^-$) figure (1) (12).

**Figure 1** The functions of co-enzymeQ10 in the Respiratory Chain. Red stars indicate main sources of superoxide (O$_{2}^-$) production. (SOD) Superoxide dismutase, (GPX) glutathione peroxidase, (O$_{2}^-$) superoxide, (H$_2$O$_2$) hydrogen peroxide, (G$_3$PDH) mitochondrial glycerol-3-phosphate
Clinical application

❖ Therapeutic effect of co-enzyme Q10 in Cardiovascular diseases

Co-enzyme Q10 may have a potential advantage for subjects with cardiovascular disorders. Impaired mitochondrial function and subsequent oxidative stress has a fundamental effect in the pathophysiology of cardiovascular diseases (14). For this cause, in addition to its vital role in energy generation and its antioxidant effects, coenzyme Q10 could be considered as an auspicious candidate to prevent or management of cardiovascular disease. The review of Flowers et al. about the present data about the effect of coenzyme Q10 supplementation for the management of cardiovascular disorders indicate that despite that coenzyme Q10 has possible role for the management of current cardiovascular disorders, additional researches are required to determine whether it has an effect in the avoidance of such conditions in population have no current disorder (15). It has been noticed that low concentrations of coenzyme Q10 are linked with many disorders such as heart failure and cardiomyopathy (16). Coenzyme Q10 has an effect in the generation of energy, so its administration may have valuable properties in patients with low contractility of cardiac muscle owing to low energy condition that linked with coenzyme Q10 deficiency and result in heart failure (11).

In addition, the protective effect of coenzyme Q10 may be recognized because of its own useful effect on heart and circulation such as its desirable effect on atherosclerosis and hypertension (15). The proposed mechanism of antiatherosclerotic and antihypertensive may relate to its antioxidant effects.

In atherosclerosis, the antioxidant effect of coenzyme Q10 may diminish low density lipoprotein peroxidation (peroxidation of LDL) and improve endothelial function since the main marker for atherosclerosis is endothelial dysfunction so coenzyme Q10 may act to improve this condition (17). While in oxidative stress conditions, there is a reduction in the availability nitric oxide and this lead to vasoconstriction and increase blood pressure, co-enzyme Q10 supplementation may preserve nitric oxide (18).

Despite a clinical trial that has been carried out, further researches with a larger sample size and a longer follow up duration has required to detect whether coenzyme Q10 has a protective effect in regard of atherosclerosis & hypertension (19).

❖ Is coenzyme Q10 has role in the prevention of statins induced muscle problem/myopathy?

Statins are a vital group of drugs that is applied in the management of dyslipidemia, so they have a role in the avoidance of cardiovascular disorders. Statins are in general safe drugs, although, a diversity of muscle problem/ myopathies have reported after its administration(20). Actually, about 10.5% of statins user may have myalgia, which is the main side effect of statin therapy (21). Even though, this is a minor side effect, it may affect patient’s compliance.

The surveys among statin users suggest that about 30% of statin users discontinue their treatment because of weakness, pain in muscle, cramps, fatigue, and stiffness (22). In addition to these minor adverse effects, rhabdomyolysis a severe life threatening condition, may occur but it is extremely rare(23).
The precise mechanism of this muscle problem/myopathy have not fully detected, but among suggested mechanisms, the effect on coenzyme Q10 de nova synthesis (24). The management of hypercholesterolemia with these drugs results in a low concentrations of co-enzyme Q10 (24, 25). Statins act by inhibiting HMG-CoA reductase, the enzyme that participate in regulation of the mevalonate pathway, the main precursor in the synthesis of many important substance include cholesterol and other agents include co-enzyme Q10 (26). The consequence of coenzyme Q10 synthesis inhibition is compromise respiratory chain in the mitochondria and impairing production of energy and this may result in induction of myopathy (27).

Additionally, serum co-enzyme Q10 is carried by lipoproteins, statins-produce LDL reduction and that is another probable mechanism for co-enzyme Q10 depletion (28).

Statin therapy will discontinue according to patients complain if the possibility of rhabdomyolysis is presence. The supplementation of co-enzyme Q10 has recommended to treat and prevent myopathy induced by statin. In reality, there is a study that recommend the usage of supplemental coenzyme Q10 in all HMG-CoA reductase inhibitors users (29). Other studies reported that coenzyme Q10 supplementation in dose (30 to 200 mg/day) may reduce muscle symptoms related to usage of statin, this may act as solution instead of discontinued treatment (30, 31). On the other hand, the result of meta-analysis study and systematic review cannot detect statistically significant beneficial effect of coenzyme Q10 administration in the improvement of myopathy induced by statin (24, 28).

- The role of coenzyme Q10 in diabetic patients

Hyperglycemia is the main characteristic sign of diabetes, it has detected that the high extent of free radicals generation subsequence resultant oxidative stress, can play significant role in the pathophysiology of diabetes and diabetic-related complications (32).

Actually, increase generation of free radicals associated with exhaustion of antioxidant defense can result in increased lipid peroxidation and cellular damage, this may lead to insulin resistance and diabetic complications (33). Coenzyme Q10 is one of the most potent antioxidants and it can act as a scavenger of free radical, so the assessment of its level can consider as an indicator of oxidative stress status within the body. High blood concentration of coenzyme Q10 had been reported not only in diabetic rats, but also in pediatrics with diabetes type 1 when their co-enzyme Q10 levels compared with healthy individuals(34, 35).

Despite this high blood levels, mitochondrial levels of coenzyme Q10 in liver & heart of rats with diabetes are low. According to those, coenzyme Q10 can consider as a one of mechanisms that provide protection against oxidative stress condition. Moreover, many studies had performed to assess the promising positive effect of co-enzyme Q10 administration in diabetic patients. The complications of diabetic are linked to persist high levels of glucose, and that result in overproduction of superoxide anion in the mitochondria which acts to produce cellular and tissue damage by stimulate cell death and apoptosis (36). Cardiovascular complications are the major drawbacks of diabetes type 2 and it associated with malfunction of endothelium. When oxidative stress lead to the inhibit normal endothelial function, Many researches indicate, co-enzyme Q10 administration may enhance endothelial to produce their function properly by triggering
mitochondrial oxidative phosphorylation and endothelial nitric oxide synthase (37).

- **The effect of co-enzyme Q 10 in neurodegenerative disorders**

Mitochondrial dysfunction that produces abnormal energy metabolism, oxidative stress with its related increased oxidative damage and inflammation considers important etiologies for various neurodegenerative disorders.

The studying of antioxidant effect in the treatments of various condition is a site of interest (38). Co-enzyme Q10 is a mitochondrial function enhancer and strong antioxidant, so it could be a hopeful neuroprotectant to slow the progress of Parkinson’s, Alzheimer’s, and Huntington’s diseases, along with other neurodegenerative disorders such as Friedrich’s ataxia and amyotrophic lateral sclerosis (10, 39).

In actual fact, co-enzyme Q10 had shown a neuroprotective role in vitro, and that since it has stabilizing effect on the mitochondrial membrane of neuronal cells where they are exposed to oxidative stress. That result in to reduced cell death and/or damage, those are involved a cause of the abovementioned neurodegenerative disorders (40). In animal studies, the detected results confirm the neuroprotective effect of co-enzyme Q10 (41).

Actually, co-enzyme Q10 has the ability to defend neurons from injury by oxidation in a model of Parkinson’s and (42) Alzheimer diseases, also it decreases generation of β-amyloid plaque in vivo a in mouse model with Alzheimer disease (43) and this lead to survival and behavioral enhancement in treated mouse with frontotemporal dementia (44).

In neurodegenerative diseases, there are association with low serum levels of co-enzyme Q10, and that indicates poor antioxidant status, and a higher oxidative damage to cells and tissues.

Consequently, there is an indication for co-enzyme Q10 levels assessment to predict and follow up the development of neurodegenerative diseases, include dementia (45). Regardless of findings in animal models, that have confirmed a relationship between coenzyme Q10 and neuroprotection, until now, there are unsatisfactory evidences to support co-enzyme Q10 usage routinely in humans with neuronal problems.

In the study of Chang et al., they established that since there are no clinical trials confirmed that coenzyme Q10 has been involved in the prevention of neurodegenerative disease progression or decreased their risk, this necessitates further clinical trials carried out in order to improve therapeutic strategies for these diseases (46).

- **Liver Disease**

Despite that endogenous coenzyme Q10 production take place in all the body, the liver is the main organ responsible for co-enzyme Q10 production this because of high metabolic ability in addition to large size of liver. In liver disease condition, the metabolic ability of liver has been decreased, and this produce lower levels of co-enzyme Q10. Low levels of coenzyme Q10 have possible harmful outcome on heart. So, subjects with liver diseases like nonalcoholic fatty liver disease (NAFLD) have risk factor for cardiovascular diseases. Cardiovascular diseases have described as main causes of death in subjects with NAFLD (47). Many cardiovascular problems are associated with NAFLD, these include arrhythmias, heart failure, atherosclerosis and valve dysfunction. In alcohol related liver disease, there is a similar association with an cardiovascular disorders and increase risk of many conditions like atrial fibrillation, alcoholic
cardiomyopathy, and arterial hypertension (48).

In individuals with fatty liver disease who consuming statins, reduced concentrations of coenzyme Q10 may be a specific problem, and that in part because the inhibition of mevalonate pathway result in inhibition of cholesterol and co-enzyme Q10 synthesis. Coenzyme Q10 supplementation can act to reducing the of cardiovascular risks in subjects with liver disease, in addition it can produce liver benefit by decreasing oxidative stress and inflammation. It was expected that the main mechanisms of alcohol produces liver injury is by generate free radicals, and by the antioxidant action of co-enzyme Q10 protection of liver cells from such oxidative damage can occurred(48, 49).

Also free radicals can induce oxidative stress and this has been associated with the pathogenesis of NAFLD (50). Animal studies have confirmed the effect of coenzyme Q10 to prevent or reduce the progress of liver cirrhosis after exposure to different toxins including wide range of substance like toxic chemicals, drugs and even parasitic microorganisms (48, 51).

One study to assess the effect of coenzyme Q10 supplement on liver toxicity done by the induction of liver damage in mice via administration of paracetamol and this followed by management with coenzyme Q10 to reduce the generation of cirrhosis tissue due to its anti-inflammatory and antioxidant effect. (50). In a similar study, in rats with a high risk to develop NAFLD, supplementation with coenzyme Q10 inhibited progression to cirrhosis via reduction of oxidative stress and inflammation(52). The studies established the ability of co-enzyme Q10 to protect liver against oxidative damage induced by free radical.

Conclusion

The aim of this review is to established the ability of co-enzyme Q10 to protect liver against certain of diseases such as cardiovascular, diabetes multiuse, neurological disorders and liver disease. The oxidative damage induced by free radical mechanism.

Conflict of interest: There is no conflict of interest.

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