Chapter

Coenzyme Q10: Regulators of Mitochondria and beyond

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Abstract

The role of coenzyme Q10 (CoQ10) was relatively unknown except its involvement in the oxidative phosphorylation at electron transport chain. Recent researches revealed its association in conditions like maintenance of cardiac and pulmonary functions, regulation of cell proliferation to cancer prevention, etc. CoQ10, a potent lipophilic antioxidant, prevents the cellular biomolecules *viz.*, DNA, RNA, lipid bilayers, etc. Endogenous *de novo* synthesis will be sufficient to maintain the daily body needs; however, synthesis showed age-dependent reduction. Commercial preparations are available for oral consumption; there are even food-grade preparations for cattle, swine and poultry. A major concern with oral intake of CoQ10 was bioavailability due to its lipophilic nature. CoQ10 has been recommended for patients under continuous statin therapy as these drugs inhibit the pathway of CoQ10 biosynthesis. The use of CoQ10 in various cardiac and tumor conditions indicates that its activity is not only due to its antioxidant activity but also due to its apoptosis property. Apart from human uses, CoQ10 is now used in food animals especially broilers as they were fed with high energy dense diet there will be leakage of electrons at electron transport chain level which adversely affects the bird's performance and also used in treatment of ascites mortality.

Keywords: coenzyme Q10, antioxidant, mitochondrial regulators, reduced, cholesterol synthesis, cancer

1. Introduction

Coenzymes are the cofactors in the body, which are essential for numerous enzymatic reactions at various levels. One such enzyme is coenzyme Q10 (CoQ10) and also widely known as ubiquinone. As the name ubiquinone suggests, this coenzyme is ubiquitous in nature. However, the identification of coenzyme Q10 (CoQ10) was accidental when Crane and co-authors in 1957 [1] were involved in the investigation of the mitochondrial electron transport system, they first identified and isolated this enzyme from the beef heart. The fundamental role of CoQ10 is in the mitochondrial respiratory chain and in oxidative phosphorylation [2], for which he was awarded the Nobel Prize in Chemistry in 1978 [3]. The CoQ10 is an endogenously synthesized lipophilic compound present in all living cells (ubiquitous in nature); hence, it is also designated as ubiquinones [4]. Coenzyme Q10 (CoQ10) is a lipid-soluble compound involved in mitochondrial adenosine triphosphate (ATP) synthesis (bioenergetics) and reduces the pulmonary hypertension syndrome and ascites mortality [5]. CoQ10 does various roles along with its three important functions in the body, namely as an electron carrier in respiratory chain, antioxidant [6] and

cell signaling and gene expression [7]. These functions have practical applications in clinical practice and its use as food/feed supplementation [8]. Supplementing coenzyme Q10 is known to provide health benefits, much like nutraceuticals even in healthy individuals [9] and individuals with metabolic disorders like oxidative phosphorylation disorder [10]. CoQ10 also maintains membrane fluidity [11] and protects membranous phospholipid against peroxidation [12] and in plant photosynthesis [13]. Normal respiratory rate requires the maintenance of a high CoQ10 concentration, and even a small decrease is deleterious [14].

2. Coenzyme Q10

2.1 Is coenzyme Q10 a vitamin?

CoQ10 is similar to vitamin K in its chemical structure, but it is not considered a vitamin because it is synthesized in the body [15, 16]. All the fat-soluble vitamins (A, D, E and K) possess isoprene units in their structures. Likewise, coenzyme Q also has an isoprenoid (seen as A, D, E and K), a quinone structure (as in vitamin K) and cyclized chromanol (vitamin E). A definition to which a molecule is considered as a vitamin is as follows: an organic compound with small molecular weight, not to be synthesized in the body and supplemented through the diet; the absence of this will lead to a deficiency syndrome; converted to an active coenzyme form required for metabolic activity. Day-to-day findings make CoQ10 nearly fit into the typical definition for a vitamin. Being endogenously synthesized by all animal tissues might rule them out for a vitamin status. But vitamin D3 and vitamin C are endogenously synthesized from cholesterol and glucose, respectively, and are still given the vitamin status; hence, CoQ10 might be termed as vitamin Q as expressed by folkers. Supplementing coenzyme Q10 provides health benefits to the likes of nutraceuticals [9].

2.2 Chemistry of coenzyme Q10

CoQ10 is a 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone [16]. It contains 10 isoprene units and is the predominant form in both mammals and birds, whereas CoQ9 (9 isoprene units) is predominant in rodents [14]. Due to its lipophilic nature and higher molecular weight (863 Da), the oral bioavailability of CoQ10 is low [8]. Following absorption, it is taken up by the liver for incorporation into very low density lipoprotein (VLDL) particles before being released into circulation [6, 15]. An increase (about 160%) in CoQ10 levels in the VLDL and LDL fractions following its dietary intake. To counteract the problem of low bioavailability, currently different types of carriers like lipid emulsion of solid triglyceride, tocopherol succinate and phospholipids (Ultrasome®) [17], different cyclodextrins [18] and gel form (UbiQGel®) [19], are being tried with great success.

2.3 Biosynthesis of ubiquinone

CoQ10 is endogenously synthesized in all human and animal cells [20]. Two pathways are involved in CoQ10 biosynthesis in the body. The biosynthesis of polyprenyl side chain occurs through the mevalonate pathway. This reaction starts with acetyl-coenzyme A and ends up with farnesyl pyrophosphate (FPP). This FPP also acts as a substrate for the biosynthesis of isoprenylated proteins, dolichol and cholesterol. However, the quinone head is synthesized from either the amino acid tyrosine or the phenylalanine [21].

Major findings of coenzyme Q10 [22] are as follows:

- Coenzyme Q is distributed throughout all cell components.
- Unlike vitamins K and E, exogenous CoQ is absorbed into liver and not in other tissues.
- All the tissues in the body have the capacity to independently synthesis CoQ, but this capacity is less during developing early embryonic tissues.
- The mevalonate pathway is used by animals, plants and fungi for the synthesis of CoQ but not used by some bacteria and also for synthesis of vitamin K in mycobacteria.
- In liver, accumulation of CoQ occurs due to lower catabolism or enhanced synthesis under conditions like deficiency of vitamin A, cold stress exposure and excess thyroid secretion.
- Excesses of CoQ in liver either by endogenous synthesis or by absorption has a negative feedback mechanism to inhibit its own synthesis, which also leads to low serum cholesterol content as *de novo* synthesis of cholesterol shares the same biosynthetic pathway.

Presently, coenzyme Q10 is produced by chemical synthesis, semi-chemical synthesis or microbial conversion and is commonly available. Humans or animals fed with non-vegetarian diet will have higher CoQ10 intake and its absorption varies with the amount and uptake increases with increase in fat content. The absorption of reduced form is more than that of the oxidized CoQ10, and with its large molecular weight, about 60% of intake is excreted through the feces [23]. The yeast fermentation technique, which involves with inclusion of B vitamins in their culture, is the major form of industrial CoQ10 synthesis. Recently, CoQ10 is available as feed grade in powder form for swine and poultry but in gel form for human preparations [24, 25].

3. Therapeutic indications

3.1 Cancer therapy

CoQ10 a lipophilic antioxidant exhibits different biological activities like immune boosting, free radical scavenging and DNA protection. Studies on administration of CoQ10 have revealed promising results in prevention and/or treating cancers. Positive effect with breast cancer in patients consuming CoQ10 has been reported in recent publications [26–29].

3.2 Insufficiency of CoQ10 levels are considered as one of the risk factors

A significant lower level of CoQ10 is observed in cancerous tissues when compared to the normal tissues. CoQ10 is known for its counteraction of ROS in cellular and DNA integrity [30]. A case-control study [31, 32] revealed an inverse association between CoQ10 levels and incidence of breast cancer. An *in vitro* study with MCF-7 breast cancer cell lines where the cells were co-incubated with CoQ10 showed results with significant decrease in intracellular peroxide

formation and matrix metalloproteinase 2 activity and the effects were in a dose-dependent manner [33].

Results further showed that CoQ10 had no inhibitory effect on apoptotic, anti-growth and anti-colonization effects of doxorubicin at any doses [34]. An animal study with mammary carcinoma model revealed that administration of CoQ10 at 40 mg/kg body weight restored the normal antioxidant level [35]. Reports suggest that increasing the dose of CoQ10 to 390 mg from 300 mg for more periods revealed resolution of tumor residue without any metastases [36–38] and increased the survivability [39]. Daily intake of a combination of 100 mg CoQ10, 10 mg riboflavin and 50 mg niacin reduced the circulating tumor markers [40–46]. Consuming a combination of CoQ10 along with lipotropic factor L-carnitine reduced the tumor-related fatigue in subjects [47–50].

3.3 Coenzyme Q10 on ascites heart index (AHI) and ascites mortality

In fast-growing broilers, the impact of ascites mortality is very high (after 5 weeks of age) as the farmers are not only losing the birds but also are incurring the feeding and rearing cost by the time. Feed restriction or skip-a-day feeding is followed in broiler during finisher phase to avoid the problem of ascites, which results in poor body weight and feed efficiency. Few researchers are suggesting that ascites might be due to the bird's inability to endogenously synthesize the CoQ10 demand. To counteract this, CoQ10 was used, and in fact, the importance of CoQ10 was felt with a reduction in ascites mortality in broilers when fed with CoQ10 [51]. Then, the term ascites heart index (AHI) comes into prominence, which gives more information about the susceptibility of the birds to ascites. Ascites heart index (AHI), a sensitive index of pulmonary hypertension, is based on the relative ratio of the right ventricle to the total ventricle [52]. The AHI was further made into a more useful tool where broilers with AHI value of less than 0.27 without any fluid accumulation in abdomen are normal and those birds having AHI value more than 0.30 with fluid accumulation are pulmonary hypertensioned and prone to ascites mortality [53]. The relative heart weight of birds receiving CoQ10 at 20 mg kgG1 of diet was higher [54–58]. A reduction in AHI ratio in broilers fed with CoQ10 at 40 mg/kg of feed was noticed [59]. However, there was a lower heart weight with respect to percentage of body weight when broilers fed with 20 and 40 mg of CoQ10 [60]. Ascites mortality in broilers was reduced around 75% by CoQ10 supplementation at both 20 and 40 mg/kg of diet. But at 40 mg/kg of diet supplementation, the incidence of leg problem was high. This reduction in ascites mortality (around 40%) was observed when broilers were fed CoQ9. These studies imply that CoQ, either 9 or 10 isoprene units, is able to reduce the broiler's mortality due to ascites.

3.4 Coenzyme Q10 on lipid metabolism

Clinical human and animal studies suggested that dietary CoQ10 supplementation improved the cholesterol metabolism in mammals. Nearly 10% lower cholesterol concentration was found in heart tissue of broilers when supplemented with CoQ10 [8]. CoQ10 supplementation decreased plasma total cholesterol concentration in humans [61] and rats [62]. CoQ10 was reportedly able to suppress the hepatic cholesterogenesis in rats [63] and in hens [64]. In an experiment in layer, chicks revealed reduced hepatic total cholesterol, plasma cholesterol and very low density lipoprotein (VLDL) cholesterol concentration by supplementation of CoQ10 at 400 and 800 mg/kg feed [65]. However, the plasma HDL, LDL cholesterol and total bile acids were not influenced by CoQ10 supplementation. The reduction in cholesterol level was due to decreased enzymatic activity of

3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) in the liver, but it had no influence on the enzymatic activity of 3-hydroxy-3-methylglutaryl coenzyme A synthetase (HMGS). Dietary CoQ10 supplementation suppressed hepatic cholesterogenesis in laying hens [64] and observed a decrease in egg yolk cholesterol concentration by 7–10% on CoQ10 supplementation.

In a long-term CoQ10 feeding trial, reduced cholesterol synthesis with suppression in cholesterol catabolism was observed resulting in return of hepatic cholesterol to normal level [65]. However, long-term (0–42 days) supplementation of CoQ10 at 20 and 40 mg kgG1 reduced the levels of serum total cholesterol and serum LDL cholesterol [58, 66]. The reduction in serum LDL cholesterol due to CoQ10 supplementation was attributed to the action of reduced form of CoQ10(H2), which induces characteristic gene expression patterns, which are translated into reduced LDL cholesterol level in human subjects. However, there were no reports of increase in the HDL cholesterol levels [58, 65]. CoQ10 reduced cholesterol metabolism in the plasma of patients with myocardial infarction [67] and in diabetic rats [62]. CoQ9, a major coenzyme Q in rats, decreases plasma total cholesterol concentration and suppresses hepatic cholesterogenesis [68].

3.5 Coenzyme Q10 antioxidant properties

Under the present intensive system of poultry production especially in tropics, stresses due to environment, metabolic, managemental, etc. are inevitable, resulting in lower productivity, less nutrient retention, decreased serum and tissue vitamin level, humoral immunity (HI) and molecular changes like protein, nucleic acid denaturation and lipid peroxidation. Increased reactive oxygen species (ROS) metabolites compromise cell membrane integrity [53], which results in drip loss in muscles [60] affect keeping quality of muscles. Different nutrients and additives (like the use of synthetic amino acids, low heat increment nutrients, vitamins C, E and minerals such as selenium, zinc and magnesium or additive such as genistein and melatonin, and essential oils) are tried with varied success to counteract these stresses [69]. Aside from its role in mitochondrial bioenergetics, ubiquinone also affects membrane fluidity [11] and protects membrane phospholipids against peroxidation [12]. CoQ10 in its reduced form possesses free radical scavenging and increases total antioxidant capacity [70, 71]. CoQ10 is preferred over α-tocopherol [72] as CoQ10 enhances the activity of other enzymatic and non-enzymatic antioxidants. The serum vitamin E level was increased by CoQ10 at 20 mg/kg [7, 58]. CoQ10 shows the property of regenerating the oxidized (inactive) α-tocopherol to reduce (an active form of vitamin E) [73]. Serum or liver malondialdehyde (MDA) is a product of lipid peroxidation and serves as a biomarker for oxidative damage in lipids. This suggested the protective action on lipid peroxidation in liver mitochondria by CoQ10.

Superoxide dismutase (SOD) activity was increased in accordance with CoQ10 supplementation in broilers and in rats [74]. An increase in hepatic SOD and anti-ROS capacity in broilers was observed by CoQ10 supplementation [55]. The supplementation of CoQ10 increases the SOD activity by antagonizing nitric oxide (NO) inactivation, thereby making more NO availability for the biological function that leads to extracellular SOD gene expression. The reduced glutathione and glutathione peroxidase activity was also increased by CoQ10 at 20 mg/kg. This synergistic action of CoQ10 is possible as it acts as a primary regenerating antioxidant [75]. However, supplementation at 40 mg kgG1 of diet resulted in no effect on serum vitamin E and SOD levels. This ineffectiveness of CoQ10 at 40 mg kgG1 of diet is due to the auto-oxidation of CoQ10 resulting in higher production of mitochondrial reactive oxygen species (ROS), which leads to oxidative

stress in the body. The development of auto-oxidation was observed in birds fed higher level of CoQ10 for prolonged duration.

4. Absorption and distribution

4.1 Coenzyme Q10 absorption among body tissues

The content of CoQ10 in different body tissues is well studied in human subjects, but there are not enough studies in farm animals or birds. The highest concentration of CoQ10 was found in the most active organs like heart, kidney and liver. The CoQ10 concentration depends on a balance between inputs and outputs. Inputs are the level of CoQ10, which is endogenously synthesized, plus dietary supply and the outputs are the usage by oxidative stress and cellular metabolism. An adult human body has approximately 2 g of CoQ10, where a daily replacement of 0.5 g should be done by both endogenous synthesis and dietary means. Therefore, an average body CoQ10 content turnover rate was around 4 days and dietary supply becomes essential with impairment in endogenous synthesis. The body content of CoQ10 decreased rapidly after the age of 40 years in humans with reduced biosynthesis. CoQ10 supplementation reversed the reduced circulating CoQ10 concentrations in statin-treated subjects as statin inhibits the pathways involved in both cholesterol and CoQ10 supplementation. Various authors recommended daily intake of CoQ10 of about 30–100 mg for healthy people over 40 years and 60–1200 mg for those undergoing an adjunctive therapy for some medical conditions.

4.2 Distribution in body tissues

The CoQ10 level in human tissues varies with inappropriate nutrition, smoking and different medical conditions such as cardiomyopathy, diabetes and neurological disorder conditions [76]. Similarly in broiler chicken, the concentration of CoQ10 among different body tissues was recorded (**Table 1**) [77].

Among the organelles, larger amount of CoQ10 is found in mitochondria of heart cells (92.3–282.0 mg/kg), followed by liver (22.7–132.2 mg/kg) of cattle, swine and chicken. Being lipophilic, vegetable oils especially rape seed and peanut oils have a high content (63.5–77.0 mg/kg) of CoQ. This again proved that CoQ10 is required more by tissues that are very active.

CoQ10 to cholesterol index (QCI) is increasingly used as a measure for assessment of meat quality. QCI was used as a reliable indicator of oxidative status, and the possible oxidative stresses induced by different food ingredients and consider them as oxidant foods [8]. In simple terms, muscles with higher oxidative stress

Tissues	Concentration (mg/kg)
Heart	92.3–192
Liver	116.2–132.2
Thigh	24.2–25
Breast	7.8–17.1
Wing	11.0
Whole chicken	14–21

Table 1.
Concentration of CoQ10 in various body tissues [77].

due to either metabolic activity or food would have a reduction of QCI value. The QCI value was higher in 20 mg/kg supplemented group suggestive of low oxidative stress. Auto-oxidation of CoQ10 at 40 mg of CoQ10/kg increased muscle metabolic activity leading to reduced QCI value [78]. Due to its antioxidant property, CoQ10 supplementation will be helpful in reducing drip loss during meat storage. Supplementation with CoQ10 at 40 mg kgG1 diet improved breast muscle yield and reduced the drip loss in broilers [60]. The reduction in muscle drip loss was attributed to the reduced reactive oxygen metabolites, thereby improving the cell membrane integrity and improved water retention.

5. Conclusion

The role of coenzyme Q10 is widely being studied under various health conditions including cancer and cardiac hypertrophy. Its importance in normal healthy life is quite evident and physicians are prescribing it for oral intake for persons who continuously smoke as well as for those under statin drug therapy. Recently, CoQ10 was widely used in food animals especially broilers, which are highly susceptible to mortality due to ascites/sudden death syndrome as a result of its rapid growth rate.

Conflict of interest

The author declares no conflict of interest.

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