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Coenzyme Q10: The Cardiac Bio-energizer in Cardiovascular Diseases

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Abstract

This systematic review is aimed to identify, evaluate and summarize the role of oral Coenzyme Q10 supplementation in prevention and treatment of cardiovascular diseases (CVD). CoQ10 is concentrated primarily in the cellular mitochondria where it functions as a co-factor transferring electrons from Complex I to Complex II, III ultimately resulting in the formation of energy in the form of ATP. Coenzyme Q10 an endogenous antioxidant declines in our body because of various factors like aging, diseases and use of certain drugs like statins, beta-blockers which exacerbate its deficiency. Deficiency of this important endogenous antioxidant CoQ10 results in energy depleted state. Published data and research have suggested that Coenzyme Q10 an endogenous antioxidant has a potential for being used in the prevention and treatment of CVDs, in particular in Heart failure and Ischemic heart disease. Supplementation with CoQ10 not only corrects the deficiency of CoQ10 by improving the circulating levels of CoQ10 but also shows a significant improvement in various parameters like ejection fraction, NYHA class, symptom score and survival rate. Being a natural substance with low toxicity and good efficacy it would be appropriate to recommend CoQ10 as an adjunct to conventional therapy in selected group of patients.

Keywords: CoenzymeQ10; Cardiovascular Disease; ATP; Heart Failure; Endogenous Antioxidant; Ejection Fraction

Introduction

In the Western countries, cardiovascular disease (CVD), is considered as disease of the aged. 23% of CVD death occur below the age of 70 years, however in India a fact to worry is about the rising incidences of CVD for people between 25-69 years, to 24.8% which means the loss of productive population. An estimated 9.2 million productive years of life were lost in 2000 with an expected increase to 17.9 million years in 2030 [1]. Various CVDs like angina, myocardial infarction, heart failure and cardiomyopathies are characterized by decreased pumping action of the heart resulting in energy deprivation state which is usually present in the form of symptoms like fatigue and dyspnea. However, it is thought that the risk of CVD can be reduced by changing number of modifiable risk factors like exercise, lifestyle and diet. Dietary supplements like Coenzyme Q10 (CoQ10), have received a great deal of attention for the prevention of CVD as deficiency of CoQ10 is frequently seen in cardiovascular patients [2]. The clinical experience of CoQ10 in cardiology includes studies on heart failure, hypertension, coronary artery disease, diastolic dysfunction of the left ventricle, also inischemia-reperfusion injury as it relates to coronary artery bypass graft surgery (CABG) [3]. Coenzyme Q10 is a naturally occurring fat soluble substance present in all cells of our body with high concentration in tissues requiring high amount of energy like the heart, liver, kidney and pancreas. Coenzyme Q10 or Ubiquinone is a vital antioxidant present intracellularly that is synthesized by the human body. Coenzyme Q10 plays a vital role in energy (ATP) production in the body by acting as an electron carrier in the mitochondrial oxidative phosphorylation and as a coenzyme for mitochondrial enzymes [4]. 95% of the energy of the human body is produced in the mitochondria which are required for basic functioning of the cell like growth and maintenance. Heart, having the highest concentration of CoQ10, utilizes it for energy dependent processes like cardiac contraction and relaxation. It is also vital for the functioning of various ATP regulated membrane channels as well. Besides providing energy in the form of ATP to the heart, Coenzyme Q10 also functions as a free radical scavenger and is potentially useful in most of the cardiac diseases since there is increasing evidence that CVD may be associated with energy depletion and oxidative stress resulting in increased risk of recurrent cardiovascular events. This review gives details

of Coenzyme Q10 in various cardiovascular conditions.

Coenzyme Q10: A walk through the basic

Coenzyme Q10 was isolated in late 1950s from the mitochondria of beef heart by a leading biochemist Dr. Fredrick Crane. The name Coenzyme Q10 was coined after the discovery of its structure which consisted of a quinone ring denoted by 'Q' along with 10-isoprenoid units in its side chain denoted by '10', and since its function was acting as a coenzyme hence the name. It is also called "Ubiquinone" as it is present ubiquitously in all living beings. Coenzyme Q10 being a lipid-soluble micronutrient is endogenously synthesized in the body. Ubiquinone has a strong influence on at least three mitochondrial enzymes (complex I, II and III) as well as enzymes in other parts of cell. These enzymes are involved in oxidative phosphorylation pathway and therefore, are vital for synthesis of ATP which is useful for various cellular functions. (Figure 1)

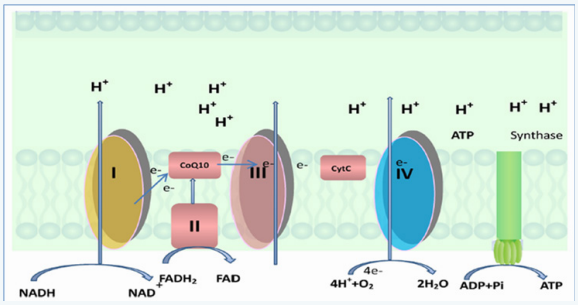

Figure 1: Coenzyme Q10 acts as an electron acceptor at the level of mitochondria.
ADP: Adenosine diphosphate; Cyt C: Cytochrome C; Pi: Inorganic phosphate

It may be useful in preventing cellular damage during myocardial ischemia and reperfusion. CoQ10 prevents the oxidation of lipoproteins (LDL cholesterol) and thereby inhibit atherosclerosis and disruption of plaque. It has demonstrated the various clinical benefits mainly due to its ability to improve ATP production, antioxidant activity and membrane stabilizing properties. These effects are beneficial in not only the treatment but even prevention of cardiac disorders. The antioxidant activity of CoQ10 confers protection against peroxidation of lipids and works together with other antioxidants like vitamin E in preventing the damage to plasma lipids and lipid membranes. CoQ10 may offer significant protection against deposition of fatty plaque (atherosclerosis) by activating smooth muscle cells in which it is abundant, and by preventing the formation of lipid peroxides and oxidation of LDL (low density lipoprotein). It might have some ability to maintain the integrity of various ion channels like sodium channels, myocardial calcium ion channels, and potassium channels during ischemic insults [5].

Coenzyme Q10: Different forms; different functions

Coenzyme Q10 is present in all membranes throughout the body. It is also present in the bilayered phospholipid membrane of all cells. The quinone head group of CoQ10 can be in the oxidized (ubiquinone) or in reduced (ubiquinol) form. Most membranes have enzyme systems that are defined to reduce the 'quinone (oxidized form)' and oxidize the 'quinol (reduced form)'. The percentage in quinol form in various membrane ranges from 30-90% depending upon the metabolic state of the cell [6]. The oxidized form of CoQ10 (Ubiquinone) helps in generation of ATP; while the reduced form of CoQ10 (Ubiquinol) acts as an antioxidant.

Sources of Coenzyme Q10

CoQ10 is present in all tissues but is highest in the heart, skeletal muscles, liver and kidney and lowest in the lungs. The normal plasma CoQ10 level in a healthy adult ranges from 0.68-1.1 µmol/L, which is maintained mainly by endogenous synthesis, and to a lesser extent by the ingestion of foods containing CoQ10 [7]. Coenzyme Q10 can be obtained by endogenous biosynthesis and dietary intake. Intracellular synthesis in human body is the major but not the only source of CoQ10. The rest can be synthesized in the liver from nourishment [8].

Endogenous Biosynthesis of CoQ10: Coenzyme Q10 is synthesized in almost all human tissues. The biosynthesis of Coenzyme Q10 is a 17-step complex process requiring at least 8 vitamins and several minerals. However, the 3 major steps are:

a. Synthesis of benzoquinone structure from either tyrosine or phenylalanine

b. Synthesis of Isoprenoid side-chain from acetyl coenzyme A (Acetyl CoA) via Mevalonate pathway

c. Condensation of the above 2 structures.

One essential step regulating the synthesis of CoQ10 seems to be the hydroxymethylglutaryl (HMG)-coenzyme A reductase reaction, common with a step in cholesterol synthesis. (Figure 2)

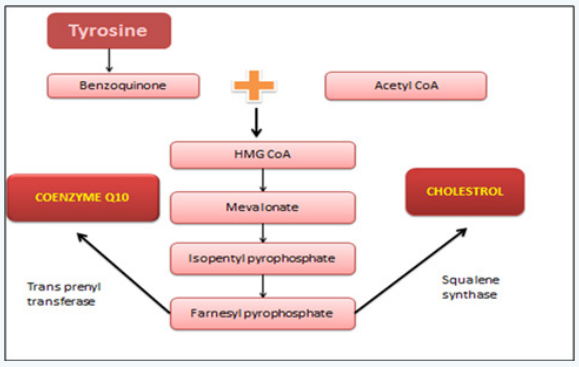

Figure 2: Coenzyme Q10: Endogenous Biosynthesis.

Dietary Sources: Coenzyme Q10 is found naturally in dietary sources. It is present in a wide variety of food from animal and vegetable sources. In animal sources, large amounts are present in organ meat like heart, liver, legs and herring. In vegetable sources, it occurs in spinach, cauliflower and whole grain but in a concentration lower as compared with meat

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and fish [9]. According to a report, dietary intake of CoQ10 in humans is approximately 2-20mg/day. Based on the food frequency study done in 1985 and 1995 by the National Food Agency of Denmark, the intake of CoQ10 from diet was found to be 3-5 mg/day in Denmark, 64 % of this daily CoQ10 originates from meat consumption [10]. In Indians the dietary intake may be 2-3 mg/day. The recommended daily intake has not yet been determined. It is possible that an intake of 10-30 mg/day is enough for healthy individuals. The South Asians have lower plasma levels of CoQ10 as compared to Caucasians and Chinese (Table 1).

Table 1: Coenzyme Q_{10}: Dietary sources.

Food	Serving	Coenzyme Q_{10} (mg)
Beef, fried	3 ounces*	2.6
Herring, marinated	3 ounces	2.3
Chicken, fried	3 ounces	1.4
Soyabean oil	1 tablespoon	1.4
Canola oil	1 tablespoon	1.0
Rainbow trout, steamed	3 ounces	0.9
Peanuts, roasted	1 ounce	0.8
Sesame seeds, roasted	1 ounce	0.7
Pistachio nuts, roasted	1 ounce	0.6
Broccolli, boiled	½ cup, chopped	0.5
Cauliflower, boiled	½ cup, chopped	0.4
Orange	1 medium	0.3
Strawberries	½ cup	0.1
Egg, boiled	1 medium	0.1

Deficiency of Coenzyme Q10

Coenzyme Q10 is synthesized by all cells in healthy individuals. The CoQ10 levels increase in first 20 years of life and thereafter we lose the ability to synthesize CoQ10 due to aging and deficiency develops. In addition to a decrease in biosynthesis, other factors or situation that may affect the level or functions of CoQ10 which include an increase in degradation or change in membrane lipids which prevent the movement of CoQ10. Another aspect causing CoQ10 deficiency is suboptimal nutrient intake. As suboptimal nutrient intake impairing CoQ10 synthesis is almost universal, deficiency of any of the vitamins or trace elements requiring CoQ10 synthesis can cause deficiency of CoQ10. Decreased absorption of nutrients necessary for synthesis of CoQ10 can be caused by aging, various diseases and use of certain prescription medications like statins, beta-blockers, anti-diabetics, etc.

Mechanism of Action of Coenzyme Q10 in various Cardiovascular diseases

a. Improvement in Cardiac bioenergetics

b. Free Radical Scavenger and antioxidant action

c. Improvement in endothelial function and vasodilation

d. Reduction in pro-inflammatory cytokines

e. Membrane stabilization action

f. Preservation of myocardial Na^+/K^+ ATPase pump

g. Anti-viscosity effect.

Coenzyme Q10: Improvement in Cardiac bioenergetics

Cardiac contraction usually happens after the release of Ca^{2+} from the sarcoplasmic reticulum (SR) which leads to activation of contractile proteins actin and myosin. During diastole, cytosolic Ca^{2+} re-sequesters in the SR. The cardiac contraction and re-uptake of Ca^{2+}in the SR is an energy dependent process requiring ATP. Myocardial relaxation that is dependent on active Ca^{2+} uptake by sarcoplasmic reticulum is an active process. Rather, this step requires more energy in the form of ATP. In cases of cardiac failure, changes in Ca^{2+} transport and metabolism have been found [11]. Myocardial failure may be related to decreased production of energy by the mitochondria. There is a decrease in availability of energy for Ca^{2+} uptake in SR (diastolic failure) and for delivery to the contractile apparatus impairing cross bridge cycling (systolic failure). As CoQ10 participates in the mitochondrial transport of electrons from organic substrates like NADH and $FADH_2$ to oxygen in the respiratory chain which leads to the production of energy, it has a role in providing energy for the functioning of the failing and energy depleted heart.

Coenzyme Q10: Antioxidant Action

Reactive oxygen species (ROS) negatively impact various vascular diseases like atherosclerosis, hypertension and diabetes mellitus and as well as in acute conditions such as hypoxia-reoxygenation states. Clinically one of the most common enzymatic sources of ROS is Xanthine Oxidase (XO) which is found to be elevated in atherosclerosis. Vascular dysfunction which is usually due pathophysiologic effects of ROS can occur through multiple mechanisms like inactivation of endothelial Nitric Oxide (NO) thereby generating peroxynitrite which results in reduced ability of vessels to relax normally. Peroxynitrite can damage lipid membrane and oxidize lipoproteins which can alter signal transduction and cause cytotoxicity. Excess level of ROS can increase platelet aggregation and adhesion and migration of monocyte [12]. Coenzyme Q10 an effective antioxidant action is a redox molecule which exists biochemically in both reduced form (ubiquinol) as well as oxidized (ubiquinone) form in biological tissues. In most cell membranes, enzymes have been

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defined that can convert ubiquinone to ubiquinol and vice-versa. Because of its important role in mitochondrial and membrane functions, the redox state of CoQ (ubiquinol/ubiquinone ratio) has been suggested to be a useful biomarker of oxidative stress [13]. In the reduced form, CoQ10 holds electrons loosely which it can give up easily neutralizing free radicals. Reduced form of CoQ10 displays the strongest antioxidant action. Various clinical studies have shown that the biomarkers of oxidative stress are decreased after CoQ10 supplementation. CoQ10 acts mainly in the mitochondria wherein its primary function is generation of ATP during the process of which few ROS are generated. It helps to quench the excessive free radicals generated that threaten cellular components such as DNA, RNA and cell membranes.

In cells, CoQ is located in the middle of the phospholipid bilayer of various membranes; however, the relative amount varies in different organelles [14].

Coenzyme Q10: Improved Endothelial Function & Vasodilation

Increased inactivation of NO by oxygen free radicals contributes to endothelial dysfunction in patients with coronary artery disease (CAD). Extracellular Superoxide Dismutase (ecSOD) is a major antioxidant present in the vessel wall is a principal regulator of endothelium-derived nitric oxide oactivity [15]. In patients with CAD, the activity of endothelium-bound ecSOD is severely reduced resulting in decreased vasodilation [16]. A clinical study has demonstrated that 1 month supplementation of 300 mg/day significantly improved endothelium dependent vasodilation and increased levels of ecSOD which is attributed to the capability of CoQ10 by counteracting NO inactivation [17].

Coenzyme Q10 : Reduction in Pro-inflammatory Cytokines

Circulating levels of tumor necrosis factor (TNF-α) interleukin-6 (IL-6) and C-reactive protein (CRP) have been linked with the risk of primary and recurrent myocardial infarction and death increases with. Various studies have highlighted important role of inflammatory mediators in the development of heart failure and acute myocardial infarction (AMI) and therefore several strategies are designed to counterbalance the different aspects of inflammatory response. In patients with CAD, supplementation of 300 mg/day of CoQ10 resulted in decrease in inflammatory markers like IL-6 & TNF-α. Anti-inflammatory effects of CoQ10 are due to the reduction of nuclear factor-kB (NF- kB). Thus, CoQ10 acts by altering the immune response [18].

Coenzyme Q10 : Role in Management of Heart Failure

Clinical background

Heart Failure (HF) a complex multifactorial syndrome is usually characterized by mechanical dysfunction of the myocardium and the inability of the heart to supply adequate amount of blood to meet the perfusion and metabolic needs of the body. Defects in bioenergetics, abnormalities of calcium homeostasis, altered signal transduction pathways, increased preload and afterload and neurohormonal dysregulation are major pathogenic factors leading to myocardial dysfunction in HF. In order to support both electrical and mechanical activities of the heart like contraction and diastolic relaxation, continuous supply of energy is needed. This requirement is fulfilled by the daily synthesis of approximately 30 kg of adenosine triphosphate (ATP) a high-energy molecule, produced mainly by mitochondrial oxidative phosphorylation. Energy deficits in the cardiac tissue have been reported in HF due to alteration in all components of cardiac energetics. Therefore, improvement in myocardial energetics becomes a promising approach to the treatment of HF [19]. Over the last few decades, clinical and experimental studies have provided substantial evidences highlighting the role of enhanced oxidative stress in HF. Excessive ROS causes cellular dysfunction, protein and lipid peroxidation, DNA damage and can lead to irreversible cell damage and death, which have been implicated in a wide range of pathological cardiovascular conditions. ROS can directly affect contractile function by modifying proteins important for excitation-contraction coupling. Moreover, ROS can also activate a broad variety of hypertrophy signaling kinases and transcription factors thereby mediating apoptosis. They also stimulate proliferation of cardiac fibroblasts and activate the matrix metalloproteinase (MMPs), leading to remodeling of the extracellular matrix. These cellular events are involved in the development and progression of maladaptive myocardial remodeling and failure [20]. Potential sources of ROS include infiltrating inflammatory cells, mitochondria, xanthine oxidase and NADPH oxidases. Excessive mitochondrial-derived cardiomyocyte ROS generation has been demonstrated in experimental models of CHF, and may be especially important for contractile dysfunction in advanced CHF. An elevation of xanthine oxidaseactivity and expression has also been reported in both human end stage CHF and canine rapid pacing-induced CHF, with the suggestion that this contributes to contractile dysfunction [21] (Figure 3).

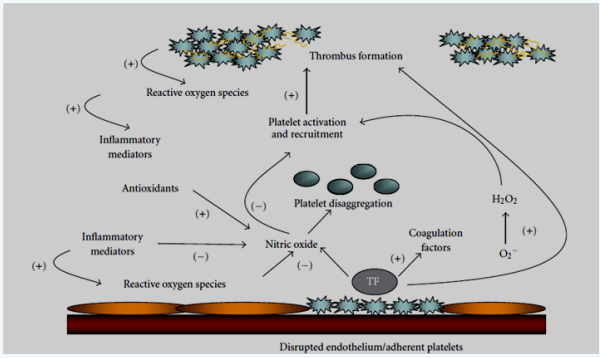

Figure 3: Coenzyme Q10: Role in Management of Heart Failure.

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In the setting of cardiovascular disease, oxidative stress is an important mediator of both dysfunctional endothelium dependent vasodilation and abnormal platelet function. Superoxide anion one of the important sources of oxidative stresses, has direct effects, and thus limits the biological activity of NO. Excessive production of vascular superoxide drives further platelet activation and recruitment leading to greater thrombus formation. The occurrence of superficial intimal injury caused by endothelial denudation and deep intimal injury caused by plaque rupture expose collagen and Tissue Factor (TF) to platelets. Local platelet activation stimulates further additional platelet recruitment and thrombus formation by supporting cell-surface thrombin formation and releasing potent platelet agonists such as adenosine diphosphate (ADP), serotonin, and thromboxane A2. Platelets aggregate via the binding of bivalent fibrinogen to GP IIb/IIIa resulting in the formation of a thrombus. NO release from the platelet influences platelet recruitment to the growing thrombus and impaired platelet-derived NO release which is likely to be associated with acute coronary and stroke syndromes. Antioxidants by scavenging of reactive oxygen species indirectly inhibit platelets. Despite the different subcellular locations of water-soluble and lipid-soluble antioxidants, these antioxidant pathways in platelets are closely linked. Antioxidants indirectly inhibit platelets through the metabolism of ROS, many of which alter platelet function. Cardiovascular disease and acute coronary syndrome have been linked Inflammation [22].

Coenzyme Q10 Deficiencies: Link with HF

Recent evidence suggests a role for CoQ10 is a predictor of outcomes and also as an adjunctive clinical therapy and therefore supplementation is routine in some countries, such as Japan. Reduced levels of specific oxidative phosphorylation and respiratory enzyme activities along with reduced energy reserve in HF are considered as some of contributing factors in the progression of disease. Low levels of CoQ10 concentration was found in 70–75% of patients with mitral stenosis or insufficiency, aortic stenosis or insufficiency, atrial septal defects, ventricular septal defects and diabetic cardiomyopathy [23]. Myocardial depletion of CoQ10 has been observed in HFpatients and the severity of this deficiency has been found to correlate with the severity of symptoms, in patients with NYHA class IV having significantly lower CoQ10 in endomyocardial biopsy samples than those in NYHA class I. In patients with cardiomyopathy this myocardial CoQ10 deficiency can be reversed by CoQ10 therapy [24]. In a recent observational study done in 236 subjects with heart failure, it was found that levels of CoQ10, but not statin therapy (known to lower CoQ10 in HF) were an independent predictor of total mortality. This CoQ10 deficiency can be detrimental to the long-term prognosis of CHF, and hence there is a rationale for controlled interventional studies with CoQ10 [25]. The concentration of CoQ10 is higher in the ventricles as compared to the atrium which presumably is ascribed to greater work burden of the ventricles and resultant greater need of energy. The concentration of CoQ10 in the normal myocardium has been measured as 0.42 μg/mg dry weight. In relation to this norm the first studies of CoQ10 concentration in plasma and myocardium showed that majority of patients with CHF had levels of CoQ10 that were below the normal and that the lower levels of CoQ10 occurred in conjunction with more severe stages of CHF (NYHA III-IV) as compared with lesser severe degrees (NYHA I-II) of CHF and with healthy persons. This correlation between NYHA categories and CoQ10 concentration in plasma and myocardium is thought to be independent of the underlying cause, since this correlation is also found in other types of CHF [26].

Summing Up: Action of Coenzyme Q10 in Heart Failure

Key substance in biological energy production (ATP), needed for both muscle contraction and relaxation.

i. Depletion of CoQ10, may be crucial in the development of HF due to an increased demand on the respiratory chain

ii. Possible restoration of the function of the exhausted myocytes in the energy-starving heart via CoQ10 supplementation

iii. Protective substance against toxic myocardial damage from metabolic inhibitors: Anthracyclines

iv. Protective effects on myocardial ischemia and reperfusion during open heart surgery ('Antioxidant' and 'Anti-ischemic' effects)

Trials in Heart Failure

From a meta-analysis of a main placebo controlled trial on CoQ10 concluded that the scores for various parameters of cardiac function was significantly better for patients given CoQ10 than for patients given placebo. An average 73% of patients treated with CoQ10 displayed improved cardiac output, 76% had increased stroke volume, and cardiac index was improved in 87%, diastolic index in 88% and ejection fraction in 92% [26].

Diastolic dysfunction which is mainly due to severe thickening of the left ventricle is one of the earliest identifiable signs of myocardial failure accounting for 30 - 49% of heart failure cases. In patients treated with 200 mg per day of CoQ10, inter-ventricular septal thickness improved significantly improving symptoms of fatigue and dyspnea with no side effects noted [27] (Figure 4).

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Author	Study design	No. of patients	NYHA class on entry	CoQ_{10} oral dosage (mg)	Treatment duration (months)	Results
Watson PS et al., 1999	Crossover	30	Unknown	33 t.i.d.	2×3	EF and SVR unaltered, left ventricular systolic and diastolic volume ↓
Khatta M et al., 2000	Two parallel groups	55	III–IV	200 q.d.	6	Exercise duration↑, EF unaltered, oxygen consumption ↑
Keogh MC Anne et al., 2003	Randomized double-blind, placebo-controlled	39	II–III Treated with ACEI	150 mg/day	3	NYHA class in the CoQ10 group: significant improvement of 0.5 class compared with the placebo ($n=18$) ($p=0.01$)..Specific Activities Scale class showed a significant ($p=0.004$) improvement in the CoQ10 group, but no change in the placebo group..6-minute walk test distance ($p=0.047$) increase in the CoQ10 group with no change in the placebo group
Belardinelli R. et al., 2006	Double-blind, placebo-controlled crossover design	23	NYHA classes II and III with stable CHF secondary to ischemic heart disease [ejection fraction 37 ± 7%]	100 mg t.i.d. with exercise training	2	As compared to exercise training (ET) plus placebo, CoQ10 plus ET showed significant improvement.CoQ10's main effect was: peak VO2 + 9%, endothelium-dependent dilation of the brachial artery (EDDBA) +38%, systolic wall thickening score index (SWTI) −12%; The combination of CoQ(10) and ET resulted in higher plasma CoQ(10) levels and more pronounced effects on all the abovementioned parameters. However, significant synergistic effect of CoQ(10) with ET was observed only for peak SWTI suggesting that ET amplifies the effect of CoQ(10) on contractility of dysfunctional myocardium.
Munkholm H. et al., 2008	Randomized double-blinded placebo-controlled	22	NYHA classes II–III with mean left ventricular (LV) ejection fraction 26%, mean LV internal diameter 71 mm	100 mg twice daily	3	A right heart catheterisation was done including a 3-minute exercise test. The stroke index at rest and work improved significantly, the pulmonary artery pressure at rest and work decreased (significantly at rest), and the pulmonary capillary wedge pressure at rest and work decreased (significantly at 1 min work).
Hosseini, 2008	Randomized placebo-controlled	50	NYHA classes II–III	100 mg daily	12	Significant increase in ejection fraction and improvement in symptoms

Figure 4: NYHA: New York Heart Asoociation; EF: Ejection Fraction; SI: Stroke Index; CI: Cardiac Index; EDVI: End Diastolic Volume Index; W: Watts; SV: Stroke Volume; CO: Cardiac Output; EDV: End Diastolic Volume; SVR: Systemic Vascular Resistance; PEP-LVET: Prejection Period-Left Ventricular Ejection Time Ratio; QOL: Quality Of Life.

A meta-analysis of CoQ10 in HF there was a 3.7% improvement in ejection fraction. Cardiac output was found to increase by 0.28 L/min. There was a trend toward an increase in SV. Stroke index increased an average of 5.68 mL/m^2 [28].

In another multicenter trial in 1,113 CHF patients, 50-150 mg/day of CoQ10 was given for 3 months (78% of patients received 100 mg/day). The proportion of patients with improvement in clinical signs and symptoms were as follows: sweating 82.4%; jugular reflex 81.5%; cyanosis 81%; pulmonary rales 78.4%; edema 76.9%; palpitations 75.7%; vertigo 73%; arrhythmia 62%; insomnia 60.2%; dyspnea 54.2%; nocturia 50.7%; and enlargement of liver area 49.3%. Fifty four percent of patients had improvement of at least 3 symptoms. Moreover, 28.8% of patients entered as NYHA class III improved in to score class II and 89.7% of patients entered in as NYHA class II improved in score to class I [29].

Q-SYMBIO Study: Alleviating Heart Failure with Coenzyme Q10

Q-SYMBIO (SYMptoms, BIOmarker) study was initiated as a result of encouraging effects of CoQ10 in heart failure and need for its further research. It was a multinational, randomized double blind, placebo controlled trial the abstract data of which was recently published in European Society of Cardiology Heart Failure Summit (2013). The aim of the study was to determine whether CoQ10 supplementation would improve survival rate and whether CoQ10 has a potential of risk reduction and to prevent complications when used as a regular supplement. 420 patients with heart failure (NYHA class III and IV) receiving current pharmacological therapy were randomly assigned in parallel groups to CoQ10 (100mg) thrice daily versus placebo. The primary long term endpoint of the study was the time to first Major Adverse Cardiac Event (MACE) including unplanned hospitalization due to worsening of heart failure, cardiovascular death, urgent cardiovascular transplantation and mechanical support. CoQ10 group, after three months showed reduced level of N-terminal pro-brain natriuretic peptide (NT-pro BNP), while significant improvement of the NYHA Class (p = 0.047) was observed at the end of two years. The primary endpoint was reached by 29 patients in the CoQ10 group, as compared with 55 patients in the placebo group. All-cause mortality was also found to be lower in the CoQ10 group (18 patients) versus placebo (36 patients). There were fewer adverse events in the CoQ10 group compared to the placebo group (p = 0.073). Thus the patients treated with CoQ10had reduced hospital admission rates for worsening HF and lower cardiovascular death both of which may reflect a significant improvement in cardiac function. Results of the Q-SYMBIO study showed that CoQ10 fulfills various criteria of an obvious adjunct in patients with symptomatic HF along with standard therapy [30].

Clinical Implication of Coenzyme Q10 usages in patients with end-stage heart failure waiting for heart transplantation

A clinical study done in 27 patients with end-stage heart failure waiting for heart transplantation with evident symptoms of fatigue, nocturia and dyspnea showed a great improvement after supplementation with 60 mg of CoQ10 daily for 3 months. The patient showed significant improvement in clinical symptoms, functional status and quality of life of patients. This improvement was because external correction of CoQ10 levels can presumably restore the mitochondrial bioenergetics and exert an antioxidant effect, which increases the oxygen delivery to the striated skeletal muscle. The findings of this study support the efficacy of CoQ10 treatment on symptoms in patients suffering from end-stage heart failure. Hence, CoQ10 should be considered as an optional addition to regular medical regimen for the management of end stage heart failure [31].

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Coenzyme Q10 and Statins

Patients with cardiovascular diseases are usually prescribed statins for primary as well as secondary prevention of future cardiac events.

Statin supplementation leading to deficiency of CoQ10

Statins being an effective class of drug for reducing low density lipoprotein (LDL) are also associated with beneficial impact on cardiovascular morbidity and mortality. **Statins block the endogenous biosynthesis of cholesterol as well as Coenzyme Q10 by inhibiting the enzyme HMG CoA reductase, resulting in Coenzyme Q10 deficiency.** The resulting reduction in blood CoQ10 level is due to the partially shared biosynthetic mevalonate pathway of CoQ10 and cholesterol. Statins are known to reduce cholesterol/LDL levels by inhibiting HMG-CoA reductase, they can as well lower serum levels of coenzyme Q10 up to 40%. This results into depletion of CoQ10levels in patients with heart failure using statins; this may lead to significant harmful effects which can be negated by oral CoQ10 (Figure 5).

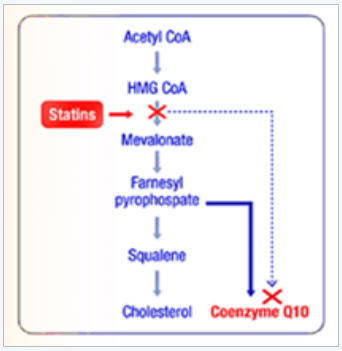

Figure 5: Statins & Coenzyme Q10 share a common biosynthetic pathway.

Benefits of Stains & Coenzyme Q10 in patients with Chronic Heart Failure (CHF):

Statins reduce the already low levels of CoQ10 present in patients with Heart failure. Coenzyme Q10 and Statins have the potential to improve cardiac function in two possible ways:

1. Coenzyme Q10 supplementation along with statins replace the statin depleted CoQ10 levels. CoQ10 also exerts its bioenergetic action by improving the efficiency of energy production (ATP) in the heart thereby improving the myocardial contractility. Various clinical trials have shown that CoQ10 improves functional capacity, symptoms, and QoL in patients with no significant side effects in patients with HF. Coenzyme Q10 supplementation also showed significant improvement in hemodynamic parameters like cardiac index, ejection fraction, stroke volume and end diastolic volume.
2. Also the combination of CoQ10 and statin has shown synergistic action on oxidative stress through activation of the enzyme superoxide dismutase that regulates nitric oxide metabolism and thus the determining step in free radical scavenging. Low markers of oxidative stress have been linked with improved cardiac function by both statins and coenzyme Q10 [32,33].

Dosage of Coenzyme Q10

Coenzyme Q10 is usually given as an adjuvant therapy in the management of various CVDs. As per various clinical trials and documented evidences, in Heart Failure the dosage of coenzyme Q10 is 100-200 mg/day which can be increased up to 300 mg/day. Coenzyme Q10 are usually given along with Statin in the dose of 100 mg/day.

Conclusion

The relationship of beneficial effects of CoQ10 in patients with congestive heart failure has been studied for decades. Early studies in patients with heart failure have reported declining myocardial level of CoQ10 with increasing severity of heart failure. Such a decline in CoQ10 levels might be exacerbated by concurrent treatment with statins and β-blockers, which can further suppress endogenous synthesis of CoQ10. Pilot clinical trials involving supplementation of CoQ10 in HF patients reported improvement in various functional parameters such as ejection fraction, stroke volume and cardiac output, with minimal side effects. Most definitively, recent Q-SYMBIO trial, a multicenter randomized placebo-controlled trial, has demonstrated the beneficial impact of supplemental CoQ10 on hard end points in HF. Thus, in conclusion, increasing evidences suggests that adjuvant supplementation of CoQ10 may be a useful option for effective management of heart failure, with the advantage of excellent clinical tolerance—reflecting its status as an essential physiological cofactor.

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