New Roles of Coenzyme Q10 in Cardiovascular Diseases, Discovered by a Single Group

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Abstract

Ubiquinone (Coenzyme Q10) is naturally present in our diet and synthesized in all body cells especially muscles. The biosynthesis of ubiquinone from the amino acid phenylalanine, tyrosine and acetyl-CoA, is a multi-stage process requiring at least eight vitamins and several phytochemicals. Coenzyme Q10 (Co Q10), is a fat soluble quinone with characteristics common to vitamins which is found in the organs of various animal species with highest concentrations in the heart, liver, kidney, muscles and pancreas. Festenstein et al in 1955 named the substance ubiquinone while Crane et al in 1957 chose the name coenzyme Q. Ubiquinone is a component of the mitochondrial respiratory chain, participating in electron transport in NADH-coenzyme Q reductase (complex I), succinate coenzyme Q reductase (complex II) and the cytochrome system. Folkers and his group determined the structure of the quinone moiety which was found identical to that described by Morton and his team, and suggested the name “ubiquinone” referring to the ubiquitous occurrence of this compound in various tissues. In 1957, Crane et al demonstrated that it has an important role as a redox carrier in the mammalian respiratory transport chain. In 1972, Littarru, of Italy and the late Prof. Folkers from Texas, documented a deficiency of CoQ10 in human heart disease, particularly among patients subjected to bypass surgery in Houston. CoQ10 deficiency has also been found in blood samples from patients with cardiovascular diseases (CVDs) and brain diseases compared with levels in healthy human subjects. Yamamura and his group were the first to use CoQ10 for the treatment of cardiovascular disease (CVD) in the 1960’s. However, Folkers et al. presented the rationale for using CoQ10 in treating congestive heart failure (CHF) (19) and Mortensen et al presented the largest trial of CoQ10 in heart failure. Gvozdjakova et al correlated brain CoQ10 with other clinical conditions. Singh’s group has demonstrated for the first time that CoQ10 can modulate plasma insulin, lipoprotein(a), serum creatinine and albuminurea, serum nitrite, serum IL-6, TNF-alpha, blood pressure variability, atherogenesis, myocardial dysfunction in myocardial infarction and neuronal degeneration, hence CoQ10 needs exploration for its supplementation in CVDs and other chronic diseases.
Introduction

Cardiovascular Diseases (CVDs) have become a major cause of morbidity and mortality in the developed and developing countries [1,2]. The increased risk of CVDs appears due to rapid changes in diet and lifestyle [3-5]. The International Atherosclerosis Society (IAS) here updates its recommendations on treatment of high level of blood cholesterol and dyslipidemia for the purpose of reducing risk for atherosclerotic cardiovascular disease (ASCVD) [6]. The sum of accumulated evidence of multiple types supports the contention that elevated LDL-C is a major target of lipid-lowering therapy. But there is growing evidence that very low density lipoproteins (VLDL) likewise promote atherosclerosis. Thus VLDL cholesterol (VLDL-C) is another potential target of cholesterol-lowering therapy. VLDL-C is especially elevated in persons with hypertriglyceridemia. The sum of LDL-C and VLDL-C includes cholesterol in all atherogenic lipoproteins and is called non-high density lipoprotein cholesterol (non-HDL-C). Therefore non-HDL-C can be considered an alternative to LDL-C as target of therapy. Non-HDL-C is more reflective of atherogenicity in persons with elevated triglycerides. It also can be accurately measured in non-fasting serum whereas LDL-C cannot be.

Total cholesterol and low density lipoprotein cholesterol (LDL) as well as non-HDL-C, become atherogenic after oxidation due to endogenous antioxidant deficiency and deficiency of antioxidants in the diet. Oxidized form of non-HDL-C which includes LDL-C as well as VLDL-C, is highly attractive to macrophages in the development of atherosclerosis. Coenzyme Q10 (CoQ10) is a natural antioxidant and bioenergetic agent present in our body which is protective against CVDs and brain degeneration [7-10]. It is crucial in the prevention of oxidation of lipids along with antioxidant enzymes, catalase and superoxide dismutase and dietary antioxidants [7]. Oxidation of high density lipoprotein cholesterol (HDL-C) may decrease the protective potential of HDL-C which may be helpful in the mechanism of atherosclerosis. This review re-emphasizes on the role of CoQ10 in atherosclerosis and other chronic diseases.

Discovery of Coenzyme Q10

CoQ10, is a fat soluble quinone with characteristics common to vitamins which is found in the organs of various animal species with highest concentrations in the heart, liver, kidney, spleen, muscles and pancreas [11-13]. Festenstein et al in 1955 named the substance ubiquinone [12] while Crane et al in 1957 chose the name coenzyme Q [14]. Coenzyme Q10 (CoQ10) exists in three redox states in organism: fully oxidized (ubiquinone), radical (semiquinone) and fully reduced (ubiquinol). (Figure 1.)

Mitochondrial CoQ10 function as a component of the mitochondrial respiratory chain, regulate electrons transport from NADH-coenzyme Q reductase (complex I), succinate coenzyme Q reductase (complex II) and passing them to complex III [14,15], resulting in ATP synthesis. As an alternative coenzyme Q function is possible in regulation of permeability transition pore opening (in porin) and CoQ uptake through Voltage Dependent Anion Channel (VDAC) of outer mitochondrial membrane (Figure 2), [18, 19].

Folkers and his group determined the structure of the quinone moiety which was found identical to that described by Morton and his team, and suggested the name “ubiquinone” referring to the ubiquitous occurrence of this compound in various tissues including brain [12-16].

In 1957, Crane et al demonstrated that it has an important role as a redox carrier in the mammalian respiratory transport chain [14]. A high concentration of CoQ10 observed in healthy human myocardium has led to the assumption that a myocardial deficiency of CoQ10 is detrimental to cardiac function [20]. In 1972, Littarru, of Italy and the late Prof. Folkers from Texas, documented a deficiency of CoQ10 in human heart disease, particularly among patients subjected to bypass surgery in Houston, USA [21-23].
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Figure 1. Chemical structures of CoQ10.

(Lambrecht P., Kaneka, 2011)

Figure 2. Proposed novel Coenzyme Q binding site in Voltage Dependent Anion Channel of outer mitochondrial membrane.

Legend:
CoQ – Coenzyme Q; VDAC – Voltage Dependent Anion Channel; ATP – adenosine triphosphate; ADP – adenosine diphosphate; Pi – inorganic phosphate; I, II, III, IV, V - respiratory chain complexes; H⁺ - proton; e⁻ - electron; Q-cycle – Coenzyme Q cycle; cyt c – cytochrome c; NADH - reduced nicotinadenindinucleotid; NAD⁺ - nicotinadenindinucleotid; FADH₂ – reduced flavinadenindinucleotid; FAD - flavinadenindinucleotid; O₂⁻ - superoxide radical; H₂O₂ – hydrogen peroxide; OH – hydroxyl radical; H₂O – water; O₂ – oxygen;
Brain coenzyme Q10 (CoQ10) concentration can influence the activity of several brain regions, including those which participate in the regulation of cardiovascular circadian rhythms, food intake, neuroendocrine stress response, and sleep regulation [16]. However, the effect of supplemented ubiquinol (reduced CoQ) into brain regions was not known. Previous our study determined baseline levels of ubiquinone (oxidized CoQ) in various rat brain regions and proved the bioavailability of the liposomal ubiquinol to selected brain regions after its administration into right brain ventricle. Our data indicate that administration of ubiquinol may create the basis for modulation of neuronal activities in specific brain regions (Figures 3-9), [17].

Maximum CoQ10-OX concentration (compared with group without ubiquinol administration – time zero minutes) was found after 15 minutes in the following brain regions: nucleus supraopticus (NSO), nucleus suprachiasmaticus (NSCH), nucleus ventromedialis (NVM), nucleus dorsomedialis (NDM) and locus coeruleus (LC). After 60 minutes, the maximum CoQ10-OX concentration was found in basal ganglia (BG), nucleus paraventricularis (PVN) and cortex (CX), while after 120 minutes in organum vasculosum laminae terminalis (OVLT) and in substantia nigra (SN).

Administered ubiquinol increased CoQ9-OX concentration in OVLT, nucleus tractus solitarii (NTS) and A5 noradrenergic cell group (A5) after 120 minutes and had no effect on CoQ9-OX concentration in NVM, NDM and CX. These data show higher baseline concentrations of CoQ9-OX than of CoQ10-OX in rat brain regions BG, OVLT, SN, CX, NTS, A5, but lower in NSCH, NVM, NDM and LC. These different CoQ10 levels could be correlated with individual brain region functions. The benefit of therapeutic supplementation of ubiquinol in neurodegenerative diseases depends also on its bioavailability. It has been demonstrated for the first time that ubiquinol has beneficial effects on psychological manifestation in children with autism [16].

CoQ10 deficiency has also been found in blood samples from patients with cardiovascular diseases (CVDs) compared with levels in healthy human subjects [22-25]. Yamamura and his group were the first to use CoQ10 for the treatment of cardiovascular disease (CVD) in the 1960’s [24]. However, Folkers et al. presented the rationale for using CoQ10 in treating congestive heart failure (CHF) [21] and Mortensen et.al presented the largest trial of CoQ10 in heart failure (25).

Ubiquinone is naturally present in our diet and synthesized in all body cells especially muscles. The biosynthesis of ubiquinone from the amino acid phenylalanine, tyrosine and acetyl- CoA, is a multistage process requiring at least eight vitamins and several phytochemicals [7]. It is reasonable that deficiency of any of these micronutrients may result into ubiquinone deficiency. Ramasarma studied the natural occurrence of ubiquinone and its distribution in the body [24]. Stocker and coworkers reported that ubiquinol-10 protects human low density lipoprotein more efficiently against lipid peroxidation than does alpha-tocopherol [26]. Since then, clinical reports worldwide have described favourable effects of both intravenous and oral CoQ10 in patients with CVDs of various etiologies [27-29]. CoQ10 is a potential antioxidant and bioenergetic agent. There is evidence that CVDs and other chronic diseases may be associated with oxidative stress and deficiency of antioxidant vitamins and minerals resulting in to increased risk of recurrent cardiovascular events and other non-communicable diseases [30-32].

CoQ10 and antioxidant selenium were administered in patients with acute myocardial infarction in 1994 [33]. Finally, Singh et al. studied the effects of oral treatment with coenzyme Q10 (120 mg/d) compared with placebo for 28 days in 73 (intervention group A) and 71 (placebo group B) patients with acute myocardial infarction (AMI) [34]. After treatment, angina pectoris (9.5 vs. 28.1), total arrhythmias (9.5% vs. 25.3%), and poor left ventricular function (8.2% vs. 22.5%) were significantly (P < 0.05) reduced in the coenzyme Q group than placebo group. Total cardiac events, including cardiac deaths and nonfatal infarction, were also significantly declined in the Co Q10 group compared with the placebo group (15.0% vs. 30.9%, P < 0.02).
Regulation: cognitive function (CX), immune reactions (PVN), food intake (NVM, NDM), attention, stress (LC), circadian rhythms (NSCH), motor functions (BG, SN)

Figure 3. Bioavailability of Ubiquinol by selected rat brain regions [16].

Figure 4. LOCUS COERULEUS (LC) [17] Q10-OX, Q9-OX.

Figure 5. BASAL GANGLIA (BG) [17] Q10-OX, Q9-OX.
Figure 6. SUBFORNICAL ORGAN (SFO) [17] Q_{10-OX}, Q_{9-OX}.

Figure 7. NUCLEUS SUPRACHIASMATICUS (NSCH) [17] Q_{10-OX}, Q_{9-OX}.

Figure 8. NUCLEUS DORSOMEDIALIS (NDM) [17] Q_{10-OX}, Q_{9-OX}. 
The extent of cardiac disease, elevation in cardiac enzymes, and oxidative stress at entry to the study were comparable between the two groups. Lipid peroxides, diene conjugates, and malondialdehyde, which are indicators of oxidative stress, showed a greater reduction in the treatment group than in the placebo group. The antioxidants vitamin A, E, and C and beta-carotene, which were lower initially after AMI, increased more in the Co Q10 group than in the placebo group. These findings suggest that Co Q10 can provide rapid protective effects in patients with AMI if administered within 3 days of the onset of symptoms. More studies in a larger number of patients and long-term follow-up are needed to confirm our results.

Effect of hydrosoluble CoQ10 causing a decline in insulin levels in hypertensive patients with coronary artery disease have been reported by Singh’s group for the first time in the literature [35]. Treatment with coenzyme Q10 (60 mg twice daily) were compared in a randomized trial, for 8 weeks in 30 (coenzyme Q10: group A) and 29 (B vitamin complex: group B) patients known to have essential hypertension and presenting with coronary artery disease (CAD). After the follow-up, the following indices were reduced in the coenzyme Q10 group: systolic and diastolic blood pressure, fasting and 2-h plasma insulin, glucose, triacylglycerol, lipid peroxides, malondialdehyde and diene conjugates. The following indices were increased: HDL-cholesterol, vitamins A, C, E and beta-carotene (all changes P<0.05). The only changes in the group taking the B vitamin complex were increases in vitamin C and beta-carotene (P<0.05). These findings indicate that treatment with coenzyme Q10 decreases blood pressure possibly by improving insulin insensitivity by decreasing oxidative stress and insulin response in patients with known hypertension receiving conventional antihypertensive drugs.

A reduction in serum concentration of lipoprotein (a) among acute myocardial infarction (AMI) patients was also observed for the first time by Singh et al in 1999 [35]. Subjects with clinical diagnosis of AMI, unstable angina, angina pectoris (based on WHO criteria) with moderately raised lipoprotein (a) were randomized to either coenzyme Q10 as Q-Gel (60 mg twice daily) (coenzyme Q10 group, n=25) or placebo (placebo group, n=22) for a period of 28 days. Results: Serum lipoprotein (a) showed significant reduction in the coenzyme Q10 group compared with the placebo group (31.0% vs 8.2% P<0.001) with a net reduction of 22.6% attributed to coenzyme Q10. HDL-C showed a significant increase in the intervention group without affecting total cholesterol, LDL cholesterol. Coenzyme Q10 supplementation was also associated with significant reductions in blood glucose, thiobarbituric acid reactive substances (TBARS), malondialdehyde (MDA) and diene conjugates, indicating an overall decrease in oxidative stress.

In view of the above beneficial effects of CoQ10 on vascular disease risk [37-40], Singh et al
demonstrated for the first time in rabbits, that CoQ10 can inhibit atherosclerosis and modulate the quality and chemical composition of atheroma [38]. The effects of the administration of coenzyme Q10 (3 mg/kg per day) (group A, n=10) and placebo (aluminum hydroxide, 3 mg/kg per day) (group B, n=10) were compared over 24 weeks in a randomized, single-blind, controlled trial. There were two groups of rabbits receiving a trans fatty acid (TFA)-rich diet (5-8 g/day) for 36 weeks. Oxidized rabbit chow with vitamin C plus ferric chloride was administered for 4 weeks in all rabbits. Intervention with coenzyme Q10 after feeding of TFA-rich diet was associated with a significant decline in TBARS, diene conjugates and MDA, and an increase in plasma levels of vitamin E in the coenzyme Q group compared to placebo group. These changes, which were indicators of a decrease in oxidative damage, were independent of lipid lowering. The aortic and coronary artery plaque sizes, coronary atherosclerosis index, aortic and coronary atherosclerosis scores were significantly lower in the coenzyme Q group than placebo group. Aortic and coronary plaque frequencies, as well as frequencies of ulceration, thrombosis or hemorrhage, and cracks and fissures, were also significantly lower in the coenzyme Q group, indicating a better quality of atheroma compared to those in the control group. Aortic cholesterol, triglycerides and sudanophilia were significantly lower and vitamin E significantly higher in the coenzyme Q group in comparison to the placebo group indicating that coenzyme Q10 can have beneficial effect on the chemical composition and quality of atheroma independent of hypolipidemic agents.

This group also administered CoQ10 in other CVDs, as well as in conjunction with taurine [39, 40]. In a randomized, double-blind, controlled trial, the effects of oral treatment with coenzyme Q10 (CoQ10, 120 mg/day), a bioenergetic and antioxidant cytoprotective agent, were compared for 1 year, on the risk factors of atherosclerosis, in 73 (CoQ, group A) and 71 (B vitamin group B) patients after acute myocardial infarction (AMI). After 1 year, total cardiac events (24.6 vs. 45.0%, p < 0.02) including non-fatal infarction (13.7 vs. 25.3%, p < 0.05) and cardiac deaths were significantly lower in the intervention group compared to control group. The extent of cardiac disease, elevation in cardiac enzymes, left ventricular enlargement, previous coronary artery disease and elapsed time from symptom onset to infarction at entry to study showed no significant differences between the two groups. Plasma level of vitamin E (32.4 +/- 4.3 vs. 22.1 +/- 3.6 umol/L) and high density lipoprotein cholesterol (1.26 +/- 0.43 vs. 1.12 +/- 0.32 mmol/L) showed significant (p < 0.05) increase whereas thiobarbituric acid reactive substances, malondialdehyde (1.9 +/- 0.31 vs. 3.1 +/- 0.32 pmol/L) and diene conjugates showed significant reduction respectively in the CoQ group compared to control group. Approximately half of the patients in each group (n = 36 vs. 31) were receiving lovastatin (10 mg/day) and both groups had a significant reduction in total and low density lipoprotein cholesterol compared to baseline levels. It is possible that treatment with CoQ10 in patients with recent MI may be beneficial in patients with high risk of atherothrombosis, despite optimal lipid lowering therapy during a follow-up of 1 year. Adverse effect of treatments showed that fatigue (40.8 vs. 6.8%, p < 0.01) was more common in the control group than CoQ group.

Effects of coenzyme Q10 in new indications with antioxidant vitamins deficiency were also reported by Singh et al for the first time, showing beneficial effects in patients with motor neuron disease and tuberous sclerosis as well as seizures and chronic renal failure [41]. Congestive heart failure may be associated with CoQ10 deficiency as well as with carnitine deficiency [42, 43]. In a randomized, double blind controlled trial; Singh’s group administered both the agents in patients with heart failure for the first time as metabolic treatment of heart failure [42, 43]. After a follow up period of 12 weeks, there was a significant improvement in ejection fraction and other parameters of heart failure [42]. Serum concentration of IL-6 and TNF-alpha, that are pro-inflammatory cytokines, showed a significant decline in the intervention group compared to control group which was again a novel discovery for CoQ10. Baseline serum CoQ10 (0.21±0.11 v/s 0.19+0.10ug/ml) was low, however, after 12 weeks, serum CoQ10 showed a significant increase in the carni Q-gel group compared to the control group (2.7±1.2 v/s 0.76±0.14
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167 ug/ml) [42, 43]. Serum nitrite which is is a indicator of nitric oxide showed significant increase in the CoQ10 group compared to control group.

Long-term follow up, after treatment for 12 months, the quality of life visual analogous scale revealed that dyspnea, palpitation and fatigue and NYHA class II-III-IV, which were present at rest, in all the patients, at baseline, showed beneficial effects in the intervention group compared to the placebo group [43]. The deaths (3 vs. 8) and hospitalizations due to worsening of heart failure (2 vs. 11) among intervention and control group respectively, were significantly lower in the carni Q-gel group compared to the control group (5 vs. 19, P<0.02). Treatment with carni Q-gel was stopped after 12 months. Follow up after another 3 months (total 15 months) revealed that there was a worsening of NYHA class heart failure, as well as in the quality of life symptom scale and physical performance, assessed by 6-min walk test. There was a non-significant increase in hospitalizations in the intervention group after cessation of carni Q-gel softgels, compared to hospitalizations during the last 3 months. The findings indicated that treatment with ubiquinol + L-carnitine fumarate can cause a significant improvement in the quality of life, exercise capacity, as well as improvement in The New York Heart Association (NYHA) Functional Classification, which became worst after cessation of CoQ10.

Singh et al also administered CoQ10 in chronic renal failure [44, 45]. Ninety-seven patients (mean age, 48 years) with chronic renal failure (serum creatinine > 5 mg/dl), with a history of declining renal function for at least 12 weeks, were randomly assigned to receive, in double-blind fashion, (CoQ10; 60 mg, 3 times per day orally) (Q-Gel) or placebo for 12 weeks [45]. The 45 patients who were receiving haemodialysis at the start of the study were encouraged to decrease the frequency or stop dialysis if there was an increase in urine output and a decrease in serum creatinine of more than 2 mg/dl. In the patients receiving haemodialysis and CoQ10, the mean serum creatinine concentration decreased from 9.5 to 6.7 mg/dl; mean blood urea nitrogen (BUN) decreased from 88.2 to 79.8 mg/dl; mean creatinine clearance increased from 40 to 54.9 ml/min; and 24-hour urine output increased from 1,300 to 1,920 ml. Renal function tended to worsen in haemodialysis patients receiving placebo, and the differences in the changes between groups were significant (p < 0.01 to p < 0.001). Significant improvements in each of these parameters relative to the placebo group were also seen in the non-dialysis patients treated with CoQ10. The number of patients receiving dialysis decreased from 21 to 12 in the CoQ10 group, and remained unchanged at 24 in the placebo group (p < 0.02). Eighty-one percent of the patients receiving CoQ10 had a positive response to treatment.

In a recent study, cerebrospinal fluid (CSF) concentrations of Co Q10 have been reported as breaking news finding in humans indicating that this biomarker can be used for diagnosis in the diseases of the brain [46]. Effects of Co Q10 administration in amyotrophic lateral sclerosis (ALS) have been reported again by Kawasaki et al with beneficial effects [47]. In a further study, two patients presented with positive hepatitis B virus antigen reactivity [48]. Both the patients had medical records indicating clinical and biochemical manifestations of viral hepatitis. Treatment with coenzyme Q10 and w-3 fatty acids was associated with reversal of antigenicity causing negative hepatitis B antigen reactivity, an observation made for the first time in the literature. Endothelial dysfunction in type 2 diabetes and the possible impact on this condition of CoQ10, other antioxidants and nutritional supplements may be interesting [9, 49]. The effect of CoQ10 on endothelial dysfunction in ischaemic heart disease by Tiano et al, together with recent data highlighting that treatment with CoQ10 increases extracellular SOD activity indicate that this therapy can improve endothelial dysfunction [9]. In a randomized, double blind, placebo controlled trial, the effect of coenzyme Q10 (Co, Q10, 120 mg/day) (2cap BD, n=101) and placebo containing inert fibre (500mg, cap BD, n=99) were compared in patients with acute stroke, during a follow up period of 4 weeks [8]. The diagnosis of stroke was proven by computerized axial tomography (CAT) scan in all the patients. In 28 patients, plasma coenzyme Q was determined by HPLC showing low mean levels compared to healthy control subjects (CoQ 0.21 vs. 0.27ng/ml, P<0.05). The proportion of brain haemorrhage (27.7 vs. 25.2%, n=27 vs. 25) and cerebral infarction (73.2 vs. 74.7%, n=74 vs. 74) were comparable respectively. Approximately half of the patients presented with coma grade IV in association
with hemiplegia in both the groups and rest half had hemiparesis. The proportion of deaths (13.8% vs.
18.2%, 12 vs. 15) was slightly lower in the CoQ group and all accept 2 deaths in infarction,(control group),
the deaths were in patients with brain haemorrhage, during the follow up of 4 weeks. These findings have
also been confirmed in other studies (25, 47-50). Blood pressure variability appears to be a target for
future cardiovascular protection which can be modulated by CoQ10. Coenzyme Q10 decreases all-
cause mortality by half, according to the results of a multicentre randomized double blind trial presented at
Heart Failure 2013 congress at Lisbon [23].

Table 1. Possible mechanisms of action of coenzyme Q10

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It is the first drug to improve heart failure mortality in over a decade and should be added to standard
treatment, according to lead author Professor Svend Aage Mortensen (Copenhagen, Denmark). Singh’s
group recruited 110 patients from India to Q-SYMBIO Trial [23].

In brief, Singh’s group has demonstrated for the first time that CoQ10 can modulate plasma insulin,
lipoprotein(a), serum creatinine and albuminurea, serum IL-6, TNF-alpha, serum nitrite, blood pressure
variability, acute myocardial infarction and atherogenesis and neuronal degeneration, hence
CoQ10 needs exploration for its supplementation in CVDs and other chronic diseases.

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