

New Developments in Coenzyme Q10 Research Contributed by A Single Group. Editorial

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Abstract: Coenzyme Q10 (CoQ10), first identified by Moor *et al* in 1940, is a fat soluble quinone with characteristics common to vitamins [1]. It is found in the organs of various animal species with highest concentrations in the heart, liver, kidney, muscles and pancreas [2, 3]. Festenstein *et al* in 1955 named the substance ubiquinone [2] while Crane *et al* in 1957 choose the name coenzyme Q [4]. 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 [4, 5]. 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 [2-5]. It is also rich in pancreas and may be protective against type 2 diabetes [6]. In 1957, Crane *et al* demonstrated that it has an important role as a redox carrier in the mammalian respiratory transport chain [4]. 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 [7]. 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 [8-10].

Lower than normal levels of CoQ10 have also been found in blood samples from patients with cardiovascular diseases (CVDs) compared with levels in healthy human subjects [9, 10]. Yamamura and his group were the first to use CoQ10 for the treatment of cardiovascular disease (CVD) in the 1960's [11] and later Folkers *et al.* presented the rationale for using CoQ10 in treating congestive heart failure (CHF) [8].

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Ubiquinone is naturally present in our diet and synthesized in all body cells especially muscles. The biosynthesis of ubiquinone from the amino acid tyrosine is a multi-stage process requiring at least eight vitamins and several phytochemicals [12]. It is possible 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 [13]. Stocker and coworkers reported that ubiquinol-10 protects human low density lipoprotein more efficiently against lipid peroxidation than does alpha-tocopherol [14]. Since then, clinical reports worldwide have described favourable effects of both intravenous and oral CoQ10 in patients with CVDs of various aetiologies [14-16].

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 [17-19].

CoQ10 and antioxidant selenium were administered in patients with acute myocardial infarction in 1994 [20]. Finally, Singh *et al* conducted a randomized, double blind, placebo controlled trial of CoQ10 in patients with acute myocardial infarction showing significant decrease in cardiac end points for the first time in the literature [21]. Effect of hydrosoluble CoQ10 causing a decline in insulin levels in hypertensive patients with coronary artery disease and reduction in serum concentration of lipoprotein(a) among acute myocardial infarction (AMI) patients were also observed for the first time by Singh *et al* in 1999 [22, 23]. In view of these beneficial effects of CoQ10 on vascular disease risk [24-27], Singh *et al* demonstrated for the first time in rabbits that

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CoQ10 can inhibit atherosclerosis and modulate the quality and chemical composition of atheroma [25]. This group also administered CoQ10 in other CVDs in conjunction with taurine [26, 27].

Effects of coenzyme Q10 in new indications with antioxidant vitamins deficiency were also reported by Singh *et al* showing beneficial effects in patients with motor neuron disease and tuberous sclerosis as well as seizures and chronic renal failure [28]. Congestive heart failure may be associated with CoQ10 deficiency as well as with carnitine deficiency [29, 30]. 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 [29, 30]. After a follow up period of 12 weeks, there was a significant improvement in ejection fraction and other parameters of heart failure [29]. Serum concentration of IL-6 and TNF-alpha, that are proinflammatory 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 ± 0.10 ug/ml) was low, however, after 12 weeks, serum CoQ10 showed a significant increase in the carnitine Q-gel group compared to the control group (2.7 ± 1.2 v/s 0.76 ± 0.14 ug/ml) [29,30]. Serum nitrite which is an 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 analog scale revealed that dyspnea, palpitation and fatigue and New York Heart Association (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 [30]. 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 carnitine Q-gel group compared to the control group (5 vs. 19, $P < 0.02$). Treatment with carnitine 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 nonsignificant increase in hospitalizations in the intervention group after cessation of carnitine Q-gel softules, 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 [31, 32]. 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 [32]. 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 hemodialysis and CoQ10, the mean serum creatinine concentration de-

creased 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 hemodialysis 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 a breaking news finding in humans indicating that this biomarker can be used for diagnosis in the diseases of the brain [33]. Effects of Co Q10 administration in amyotrophic lateral sclerosis (ALS) have been reported again by Kawasaki *et al* with beneficial effects [34].

In a further study, two patients presented with positive hepatitis B virus antigen reactivity [35]. 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 appears to be interesting [36]. Glucagon like peptide (GLP) produced by the glucagon gene is responsible for insulin secretion. Since CoQ10 is protective against superoxide anion produced due to hyperglycemia, Table 1, it poses the possibility that CoQ10 may be protective against free radical induced damage to glucagon gene. Thus proper functioning of GLP may be useful in controlling type II diabetes mellitus [6]. DiPeptidyl Peptidase IV (DPPIV) checks the GLP, thus in order to restore the normal functioning of these, the activity of DPP IV has to be checked using DPP IV inhibitors. CoQ10 might also enhance the activity of DPP IV enzyme which needs further studies related to ligand molecule for target protein in type 2 diabetes [6]. The present studies provide new insights for efficient inhibition of DPP IV to restore the normal activity of the body overcoming the negative effects left by other drugs.

The effect of CoQ₁₀ on endothelial dysfunction in ischaemic heart disease together with recent data highlighting that treatment with CoQ₁₀ increases extracellular SOD activity indicate that this therapy can improve endothelial dysfunction [36]. In a randomized, double blind, placebo controlled trial, the effect of coenzyme Q10 (CoQ10, 120 mg/day) (2cap BD, n=101) and placebo containing inert fibre (500mg, cap BD, n=99) was compared in patients with acute stroke, during a follow up period of 4 weeks [37]. 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

Table 1. Possible Mechanisms of Action of Coenzyme Q10

1.	Repletion of CoQ10 deficiency.
2.	Antioxidant activity.
3.	Spares Vitamin E.
4.	Direct free radical scavenger <i>via</i> semiquinone species.
5.	Membrane stabilizing effect due to phospholipid protein interaction.
6.	Preservation of myocardial Na-K-ATPase activity and ATP manufacturing.
7.	Correction of mitochondrial "leak" of electrons during oxidative respiration.
8.	Induction of DT diaphorase which is an inhibitor of free radicals.
9.	Beneficial effect on prostaglandin metabolism.
10.	Inhibition of intracellular phospholipases.
11.	Stabilization of integrity of calcium ion dependent slow channels and possibly potassium channels.
12.	Spares vitamin C, A and beta carotene by decreasing their cell consumption.
13.	Reduced insulin responses in myocardial infarction.
14.	Reduced lipoprotein(a) levels in myocardial infarction.
15.	Reduction in IL-6 and TNF-alpha in heart failure.
16.	Increased serum nitrite indicator of nitric oxide.
17.	Reduced serum creatinine in chronic renal failure.
18.	Reduced albuminuria in renal failure.
19.	Improved endothelial dysfunction
20.	Increase in coenzyme Q10 in cerebro spinal fluid in meningitis and encephalitis.
21.	Inhibition of atherosclerosis. And stabilization of plaque.

(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 [36, 38-42]. It is possible that CoQ10 acts as neuro-protective agent in stroke whereas in myocardial infarction, it protects the cardiomyocytes. However, in both the conditions, endothelial dysfunction is important which is improved by CoQ10 administration. 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. 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) of the Q-SYMBIO Trial which included 110 patients from India recruited by Singh, s group in this Trial [42].

Conclusively, Singh's group has demonstrated for the first time that CoQ10 can modulate plasma insulin, lipoprotein(a), serum creatinine and albuminuria, serum IL-

6, TNF-alpha, serum nitrite, blood pressure variability and neuronal degeneration, hence CoQ10 needs exploration for its supplementation in CVDs and other chronic diseases..

CONFLICT OF INTEREST

Conflict of interest has not been declared by the authors.

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