Coenzyme Q10 (CoQ10), (ubiquinone) and it’s reduced form Ubiquinol

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Post Categories: Anti-Aging Treatments | Breast Health | Cancer Treatment and Prevention | Cardiovascular Health | Chronic and Infectious Diseases | Cognitive Function | Fatigue | Fibromyalgia | Healthy Aging Practices | Inflammation | Pregnancy and Preconception Care | Studies/Reviews | Supplements

Introduction and overview

Coenzyme Q10 (**Ubiquinine**) or (CoQ10), belongs to a family of substances called ubiquinones. Ubiquinones, also known as coenzymes Q and mitoquinones, are lipophilic, water-insoluble substances involved in electron transport and energy production in mitochondria. The reduced form (**QH2**) is called **ubiquinol. "**The fundamental role of CoQ10 in mitochondrial bioenergetics and its well-acknowledged antioxidant properties constitute the basis for its clinical applications, although some of its effects may be related to a gene induction mechanism."[87]

CoQ10 is found in small amounts in meats and seafood. CoQ10 functions as a redox-cycling agent within the cell, acting as a mitochondrial antioxidant. CoQ10 plays an important role in the production of energy within each cell of the human body. It resides in the mitochondrial membrane and is a naturally-occurring cofactor in the electron transport chain, the biochemical pathway in cellular respiration, from which ATP and most of the body's energy are derived. CoQ10 is considered essential for the health of all the body's cells, tissues, and organs, in particular the heart. CoQ10 is a key cofactor to the process that produces 95% of the energy consumed at the cellular level. Lower levels of energy in cellular mitochondria are linked to many age-related diseases including, diabetes, Parkinson's, Alzheimer's, and heart disease. Although CoQ10 is found in all human cells, its highest concentrations occur in the heart, liver, kidneys, and pancreas. It is found naturally in the organs of many mammalian species." Given that CoQ10 is naturally so widespread in the body, it is extremely safe even at high doses. Most healthy young individuals produce adequate quantities of CoQ10 to meet their bodies' needs. However, when mitochondrial bioenergetics are inhibited by a drug, like a statin, or reduced simply because of aging, or when there is a need for higher levels of CoQ10, in heart disease for example, it becomes an essential nutrient. Various studies have confirmed that as we age our body's supply of CoQ10 slowly diminishes, making CoQ 10 a vital

nutrient for anyone wishing to inhibit premature aging. The exciting *clinical* research on CoQ10 is simply remarkable. I would go as far to say is it almost criminal that Physicians do not routinely give this remarkable compound to their patients. I have witnessed in my practice miraculous effects in people with a variety of disorders, not like any other nutrient.

Ubiquinol

Coenzyme Q10 exists in both ubiquinol and ubiquinone forms, but they have very different roles to play in the body. Compared to conventional (ubiquinone) CoQ10 supplements, the benefits of ubiquinol are enormously superior. For example, a recent peer-reviewed study measured the absorption in humans supplementing with 150 mg and 300 mg of this new ubiquinol form of coenzyme Q10.[72] Based on this study far lower doses of ubiquinol produce about the same blood (plasma) levels compared with much higher doses of ubiquinone.

What may also make this form of CoQ10 so much more effective than regular CoQ10 supplements is its ability to remain biologically active in the body much longer. In a study on aged rats, blood concentrations of this new ubiquinol CoQ10 was 3.75-fold greater after eight hours compared to the same amount of conventional coenzyme Q10.[73]

A recent study on aged rats showed a 2.5 times greater anti-fatigue

effect with Ubiquinol compared to conventional CoQ10 supplements.[74]

The superior absorption and ability to remain bioavailable over a greater sustained time period may account for the unprecedented anti-senescent effects observed with new ubiquinol compared to ubiquinone.

Why combine both forms of Co Q10

Endogenous ubiquinones (UQ) such as CO Q10 are essential electron carriers in the mitochondrial respiratory chain, and the reduced ubiquinol form is a chain-breaking antioxidant, decreasing oxidative damage caused by lipid peroxidation within mitochondria. Consequently, exogenous CO Q10 is used to decrease mitochondrial oxidative damage. The proximal radical produced during mitochondrial oxidative stress is superoxide (O(2)(.-)) and the reaction between CO Q10 and O(2)(.-) to form the ubisemiquinone radical anion (UQ(.-)) may also be important for the scavenging of O(2)(.-) by CO Q10. The situation in vivo is that many CO Q10 is predominantly located in the hydrophobic membrane core, from which O(2)(.) will be excluded but its conjugate acid, HOO(.), can enter. The reactivity of CO Q10 or umbiqinol with HOO(.) has not been reported previously. Here a pulse radiolysis study on the reactions between CO Q10 /UQH(2) and O(2)(.-)/HOO(.) in water and in solvent systems mimicking the surface and core of biological membranes has been undertaken. O(2)(.-) reacts very rapidly with CO Q10, suggesting that this may contribute to the scavenging of O(2)(.-) in vivo. In contrast, umbiquinol reacts relatively slowly with HOO(.), but rapidly with other oxygen- and carbon-centered radicals, indicating that the antioxidant role of Umbiquinol is mainly in preventing lipid peroxidation. [75]

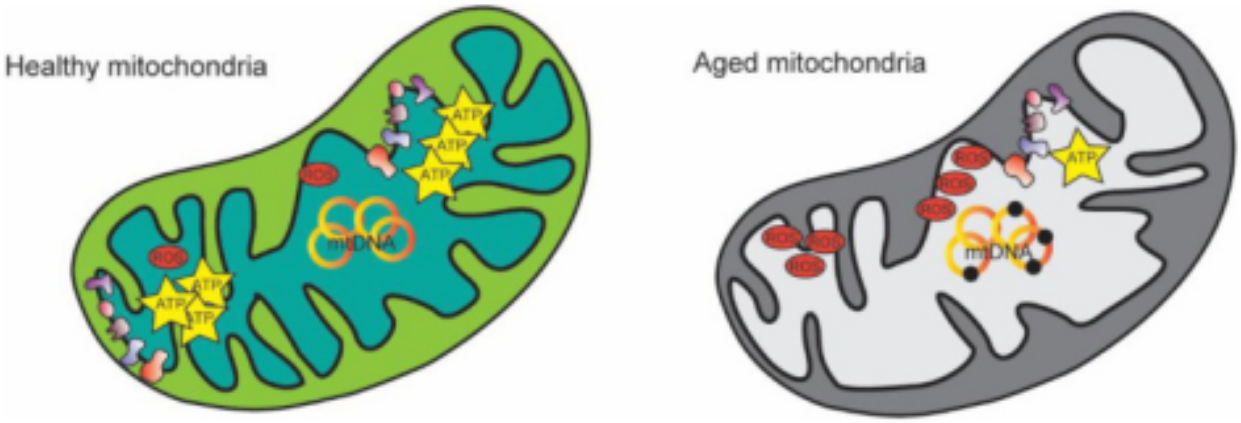
Understanding and reviewing the immense benefits of Co Q supplementation

At the inner mitochondrial membrane level, coenzyme Q is recognized as an obligatory co-factor for the function of uncoupling proteins and a modulator of the transition pore. Furthermore, recent data reveal that CoQ10 affects expression of genes involved in human cell signaling, metabolism, and transport and some of the effects of exogenously administered CoQ10 may be due to this property. Coenzyme Q is the only lipid soluble antioxidant synthesized endogenously. In its reduced form, CoQH2, ubiquinol, inhibits protein and DNA oxidation but it is the effect on lipid peroxidation that has been most deeply studied. Ubiquinol inhibits the peroxidation of cell membrane lipids and also that of lipoprotein lipids present in the circulation. Dietary supplementation with CoQ10 results in increased levels of ubiquinol-10 within circulating lipoproteins and increased resistance of human low-density lipoproteins to the initiation of lipid peroxidation. Moreover, CoQ10 has a direct anti-atherogenic effect, which has been demonstrated in apolipoprotein E-deficient mice fed with a high-fat diet. In this model, supplementation with CoQ10 at pharmacological doses was capable of decreasing the absolute concentration of lipid hydroperoxides in atherosclerotic lesions and of minimizing the size of atherosclerotic lesions in the whole aorta. Whether these protective effects are only due to the antioxidant properties of coenzyme Q remains to be established; recent data point out that CoQ10 could have a direct effect on endothelial function. In patients with stable moderate CHF, oral CoQ10 supplementation was shown to ameliorate cardiac contractility and endothelial dysfunction. Recent data from our laboratory showed a strong correlation between endothelium bound extra cellular SOD (ecSOD) and flow-dependent endothelial-mediated dilation, a functional parameter commonly used as a biomarker of vascular function. The study also highlighted that supplementation with CoQ10 that significantly affects endothelium-bound ecSOD activity. There was significant correlation between increase in endothelial bound ecSOD activity and improvement in FMD after CoQ10 supplementation. The

effect was more pronounced in patients with low basal values of ecSOD. Finally, Co Q 10 improves seminal fluid integrity and sperm cell motility. [71]

CoQ_{10} and Resveratrol Effects to Ameliorate Aged-Related Mitochondrial Dysfunctions

Mitochondria participate in the maintenance of cellular homeostasis. Firstly, mitochondria regulate energy metabolism through oxidative phosphorylation. In addition, they are involved in cell fate decisions by activating the apoptotic intrinsic pathway. Finally, they work as intracellular signaling hubs as a result of their tight regulation of ion and metabolite concentrations and other critical signaling molecules such as ROS. Aging is a multifactorial process triggered by impairments in different cellular components. Among the various molecular pathways involved, mitochondria are key regulators of longevity. Indeed, mitochondrial deterioration is a critical signature of the aging process.



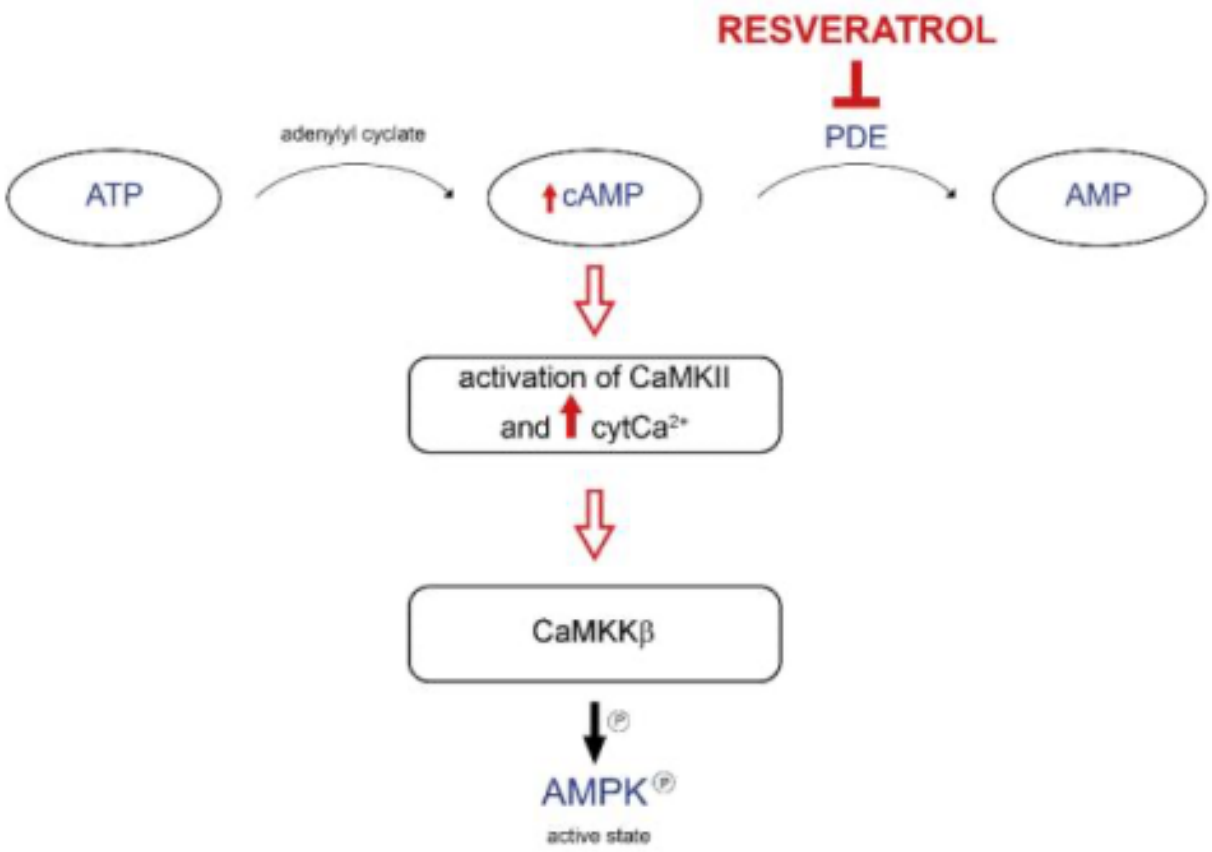
Mitochondrial changes during aging. Mitochondria display morphological and functional remodeling including abnormal cristae, decreased ATP production, increased mtDNA mutations, and alteration in ROS production.

Peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) is considered the master regulator of mitochondrial biogenesis, acting as a transcriptional activator of several gene pathways controlling a variety of mitochondrial activities, including oxidative phosphorylation, fatty acid oxidation, scavenging activities, and mitochondrial dynamics.

In recent years, heightened attention has been given to natural compounds that modulate mitochondrial function. One of the most famous is resveratrol due to its ability to increase mitochondrial biogenesis and work as an antioxidant agent.

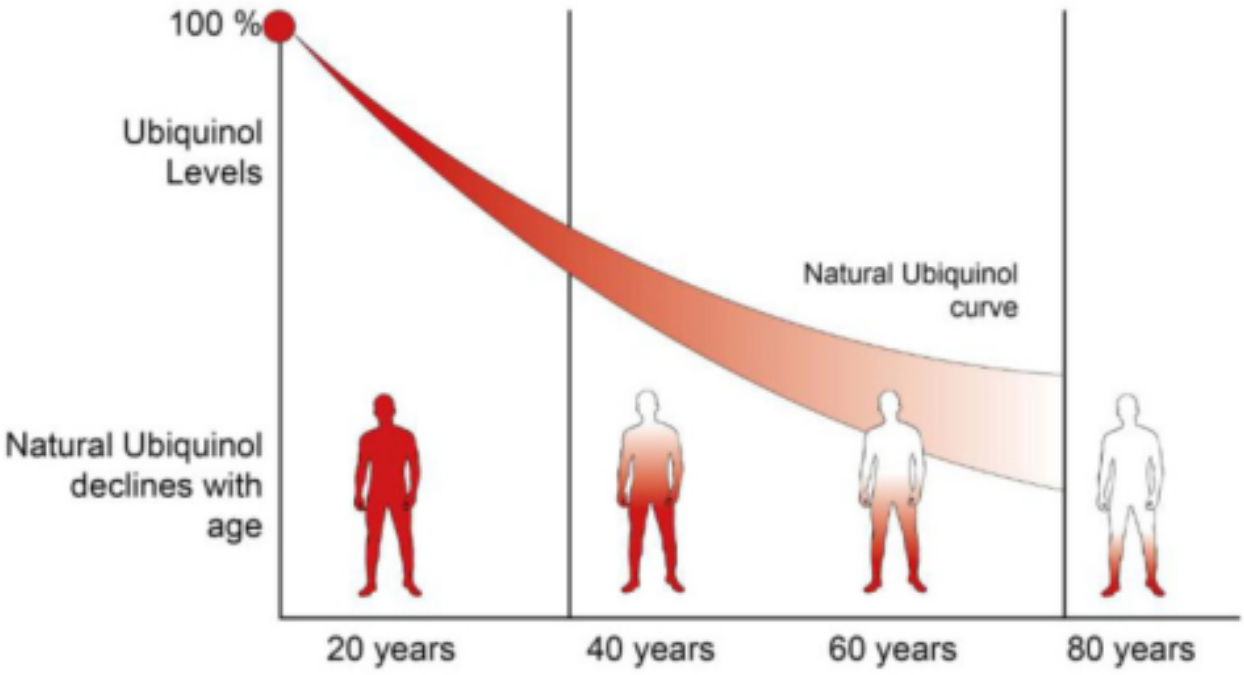
Studies related to resveratrol treatment in different physiopathological conditions.

Effects of Resveratrol On	Beneficial Effect On	Studies On	Ref.
skeletal muscle	muscle mass	rodents	[52]
	muscle performance	rodents	[53]
	sarcomere structure	rodents	[54]
	activation of AMPK-SIRT1 pathway	humans	[55]
	no difference in the inflammation state	humans	[56]
cardiovascular impairment	systolic function	rodents	[61]
	renin-angiotensin axis	rodents	[62]
	aged-related mitochondrial dysfunctions	rodents	[63]
	glycemic control	T2DM patients	[65]
	decreased cholesterol levels	patients with angina	[66]
neurodegenerative diseases	increased long-term memory formation	rodents	[69]
	increased neurogenesis and vascularization	rodents	[70]
	increased cerebellar blood flow	humans	[71]
	increased memory performance	humans	[72]
	enhanced cardiometabolic markers without affecting glycemia	humans	[76]



Resveratrol is involved in the signaling pathway, which leads to AMPK activation. Resveratrol inhibits phosphodiesterases (PDE), thus increasing intracellular cAMP concentration. cAMP elevation leads to the activation of CaMKII with the consequent increase in cytosolic Ca^{2+} concentration. Ca^{2+} activates CaMKKβ, one of the upstream kinases of AMPK.

In this scenario, we will focus specifically on the age-related decrease in CoQ levels, an essential component of the electron transport chain (ETC) and an antioxidant, and how CoQ supplementation could benefit the aging process. Generally, any treatment that improves and sustains mitochondrial functionality is a good candidate to counteract age-related mitochondrial dysfunctions.



Tian and colleagues demonstrated that dietary CoQ supplementation has beneficial effects in a senescence-accelerated mouse model in terms of increased mitochondrial biogenesis. In particular, CoQ decreases sirtuins expression resulting in the activation of PCG1α.

Studies related to CoQ_{10} supplementation in different physiopathological conditions.

Effect of Coenzyme Q10 On	Beneficial Effect On	Ref.
elderly subjects	exercise performance	[109]
Parkinson's disease patients	decreased development of disability	[116]
	no effect on motor symptoms	[105,113]
cardiovascular impairment	decreased systemic blood pressure	[107]
	preventing arrhythmias in cardiac surgery-subjected patients	[114]
	increased left ventricular ejection fraction	[115]
	decreased cardiovascular events in patients with chronic heart failure	[116]
diabetes	decreased blood glucose	[117]
	no differences in glycemic control	[118]
counteracting statins side-effects	decreased muscle impairment	[122]

A 4-year CoQ_{10} supplementation in older people increased physical performance.[112]

CoQ10 and the Heart

Cardiovascular disease is still the main field of study and the latest findings confirm a role of CoQ10 in improving endothelial function. It may also be indicated to correct reduced blood levels of CoQ10 that result from the use of HMG-CoA reductase inhibitors used to treat elevated cholesterol levels. It also appears to have usefulness in the management of periodontal disease. In cardiac patients, plasma CoQ10 was found to be an independent predictor of mortality. Studies on CoQ10 and physical exercise have confirmed its effect in improving subjective fatigue sensation and physical performance and in opposing exercise-related damage. In the field of mitochondrial myopathies, primary CoQ10 deficiencies have been identified, involving different genes of the CoQ10 biosynthetic pathway; some of these conditions were found to be highly responsive to CoQ10 administration.[87]

Coenzyme Q10 supplementation improves high-intensity interval exercise performance via changes in plasmatic and salivary biomarkers of oxidative stress and muscle damage in swimmers

- Excessive production of free radicals caused by many types of exercise results in oxidative stress, which leads to muscle damage, fatigue, and impaired performance.
- CoQ10 co-supplementation (60 mg. daily) along with royal jelly improved high-intensity interval exercise (HIIE) performance in swimmers, inhibiting exercise-induced oxidative stress and muscle damage.
- The improvements in swimmers' HIIE performance were due in significant part to CoQ10 +royal jelly -induced reducing in lipid peroxidation and muscle damage in response to exercise[114]

The effect of short-term coenzyme Q10 supplementation and pre-cooling strategy on cardiac damage markers in elite swimmers

- CoQ_{10} plays a pro-oxidant role during the increase of $O_2^{\cdot-}$, turning it into H_2O_2 at the presence of superoxide dismutase enzyme in complex I and III of the respiratory chain.
- It also plays an important role in the oxidative phosphorylation by transferring electron into complex III. In the presence of antioxidant enzymes (catalase and glutathione peroxidase), H_2O_2 is transformed into H_2O as a result of which ATP is produced; otherwise, it turns into OH.
- CoQ_{10} appears to increase ATP levels by preventing the loss of adenine nucleotide pool from cardiac cells.
- CoQ_{10} prevents lipid peroxidation acting as an antioxidant, and as an indirect stabilizer of calcium channels to decrease overload or imbalance of intracellular calcium.[114]

Coenzyme Q10 and exercise training reinstate middle cerebral artery occlusion-induced behavioral deficits and hippocampal long-term potentiation suppression in aging rats

Rational: Patients experience post-stroke cognitive impairment during aging. To date, no specific treatment solution has been reported for this disorder.

Objective: The purpose of this study was to evaluate the effects of exercise training and coenzyme Q10 supplementation on middle cerebral artery occlusion (MCAO) induced behavioral impairment, long-term potentiation inhibition and cerebral infarction size in aging rats.

Methods: Fifty aging male rats underwent MCAO surgery and were randomly distributed in to the following groups: 1-Sham, 2- control, 3-Coenzyme Q10, 4- Exercise training and 5- Exercise training with Q10

supplementation (Ex + Q10). Aerobic training groups were allowed to run on a treadmill for 12 weeks. Q10 (50 mg/kg) was administered intragastrically by gavage. Morris water maze, shuttle box and elevated plus maze tests were used to evaluate cognitive function. The population spike (PS) amplitude and slope of excitatory postsynaptic potentials (EPSP) in the dentate gyrus area were recorded as a result of perforant pathway electrical stimulation.

Results: Our study showed that Q10 and aerobic training alone ameliorate spatial memory in the acquisition phase, but have no effect on spatial memory in the retention phase. Q10 and exercise training synergistically promoted spatial memory in the retention phase. Q10 and exercise training separately and simultaneously mitigated cerebral ischemia-induced passive avoidance memory impairment in acquisition and retention phases. The EPSP did not differ between the groups, but exercise training and Q10 ameliorate the PS amplitude in hippocampal responses to perforant path stimulation. Exercising and Q10 simultaneously reduced the cerebral infarction volume.

Conclusion: Collectively, the findings of the present study imply that 12 weeks of aerobic training and Q10 supplementation alone can simultaneously reverse cerebral ischemia induced neurobehavioral deficits via amelioration of synaptic plasticity and a reduction in cerebral infarction volume in senescent rats.[118]

Many studies to date have examined CoQ10 as an addition to standard medical treatments. In several studies involving hypertension and other manifestations of cardiovascular disease, there was a significant reduction in the use of concomitant drug therapies when CoQ10 was added to the treatment regimen.

It is now known that the HMG-CoA reductase inhibitors, while very effective in lowering cholesterol levels, also significantly lower levels of CoQ10. This may be particularly hazardous for patients with heart

failure, suggesting an indication for CoQ10 in many, if not all, individuals using these cholesterol-lowering drugs.

A recent review of its therapeutic benefits suggests CoQ10 may become a standard therapy for the prevention and treatment of cardiovascular disease, including angina pectoris and congestive heart failure. Congestive heart failure (CHF) and cardiomyopathy stand out in this regard. Most importantly, long-term (more than 5 years) survival of CHF patients has been shown to be improved when patients take CoQ10 compared to placebo or standard drug treatments.[1] A preliminary investigation concluded that use of CoQ10 for six years reduced mortality in cardiomyopathy patients.[2] In comparison, digitoxin has never been shown to reduce overall mortality in CHF patients.[3]

Coenzyme Q10 Supplementation Improves Biomarkers of Oxidative Stress in Adults: A GRADE-Assessed Systematic Review and Updated Meta-Analysis of Randomized Controlled Trials

- Thirty-four RCTs containing 2012 participants were included in this review
- Pooled effects of significant increase in total antioxidant capacity (TAC) (standardized mean difference: 1.83, 95%CI: [1.07, 2.59], *p* < 0.001) and significant reduction in malondialdehyde concentrations (-0.77, [-1.06, -0.47], *p* < 0.001) were shown after CoQ10 supplementation compared to placebo.[115]

Congestive Heart Failure and Cardiomyopathy

A preliminary open study showed that 100 mg daily of CoQ10 improved symptoms in 12 CHF patients. Echocardiography demonstrated a decrease in left atrial size and other indications of recovery of heart function. A larger uncontrolled study involving 2,500 CHF patients

found that 50-150 mg of CoQ10 per day resulted in significant symptomatic and objective improvement in a significant portion.[4] There were only five confirmed instances of minor side effects, and no major ones, in this study.

A double-blind study involving severely affected CHF patients supported the findings of these open trials.[5] The 641 volunteers were randomized to receive, in addition to standard drug treatments (particularly digitalis and diuretics), placebo or approximately 100 mg CoQ10 daily (2 mg/kg). The need for hospitalizations as well as episodes of pulmonary edema, arrhythmias or cardiac asthma were significantly reduced in the CoQ10 group compare to the control group. Such powerful protection against complications of CHF supports the use of CoQ10. A meta-analysis of eight studies published since 1984 further confirmed CoQ10 is valuable for treatment of patients with CHF.[6]

Deficiency of CoQ10 in heart muscle and blood has been definitively linked to several forms of cardiomyopathy, a condition that can be induced by the commonly prescribed statin drugs.[7] Ejection fraction, stroke volume, and clinical symptoms all improved significantly when patients with idiopathic dilated cardiomyopathy took 100 mg CoQ10 daily compared to placebo in one study.[8] There were no adverse effects in this trial. The greatest recovery noted was in exercise tolerance. Hypertrophic cardiomyopathy improved in seven patients in a separate study using 200 mg CoQ10 daily.[9] As noted above, long-term use of CoQ10 may reduce mortality from cardiomyopathy.

Atherosclerosis, Angina and Myocardial Infarction

CoQ10 may also help patients with complications of coronary artery disease (CAD), including angina pectoris and myocardial infarction.

The fact that CoQ10 is a potent antioxidant in plasma [10] and low-density lipoprotein (LDL) cholesterol [11] suggests it directly impedes the pathogenesis of atherosclerosis. CoQ10 was shown to be a superior antioxidant than vitamin E in LDL in one study.[12] A study in male smokers found that 90 mg CoQ10 per day for two months was insufficient to protect LDL and VLDL from oxidation, suggesting even higher doses will be necessary to obtain this benefit, at least in the population studied.[13] Other research suggests that CoQ10 works partially by decreasing vitronectin receptor expression and reduction of platelet size, both important antithrombotic actions.[14, 15] Deficiency of CoQ10 is also correlated with higher serum total and LDL cholesterol levels.[16]

Clinical trials with CoQ10 have shown it is an effective treatment for CAD and its complications. A cross-over, double-blind study randomized 12 patients to 50 mg CoQ10 three times daily or placebo.[17] Duration of exercise and time until onset of electrocardiographic signs of ischemia increased significantly when subjects were taking CoQ10 compared to placebo. There was a trend toward reduced frequency of anginal attacks and toward less use of nitroglycerin as well. A very high dose of CoQ10, 600 mg daily, has been shown to be superior to placebo and as effective as pindolol and isosorbide dinitrate in reducing onset of ST segment depression during exercise in angina patients.[18] Though lacking sufficient numbers of patients to be definitive, these studies show CoQ10 can help offset angina.

One study has also been done looking at the effects of CoQ10 on recovery after myocardial infarction (MI).[19] A total of 32 patients hospitalized for MI were given 500 mcg sodium selenite and 100 mg CoQ10 while 29 patients were given placebo. All patients received standard allopathic interventions for MI. Starting the next day the group of 32 actively treated patients were given 100 mcg selenomethionine,

15 mg zinc, 1 mg vitamin A, 2 mg vitamin B6, 90 mg vitamin C, 15 mg vitamin E, and 100 mg CoQ10 each day while the control group continued taking placebo for one year. QT interval shortening was seen significantly more often in the control than the antioxidant-treated group. There were six deaths in the control group in the year due to reinfarction compared to one death due to a problem unrelated to the heart in the antioxidant group.

Coenzyme Q_{10} Terclatrate and Creatine in Chronic Heart Failure: A Randomized, Placebo-Controlled, Double-Blind Study

Oral supplementation with coenzyme Q_{10} (CoQ_{10}) and creatine may reduce mitochondrial dysfunction that contributes to impaired physical performance in CHF.

Methods:

We conducted a randomized, double-blind, placebo-controlled trial to determine the effect of a mixture of water-soluble CoQ_{10} (CoQ_{10} terclatrate; Q-ter) and creatine on exercise tolerance and health-related quality of life. Exercise tolerance was measured as total work capacity (kg·m) and peak oxygen consumption (VO_2, mL/min/kg), both from a cardiopulmonary exercise test. Health-related quality of life was measured by the Sickness Impact Profile (SIP) in CHF secondary to left ventricular systolic dysfunction (left ventricular ejection fraction ≤ 35%). After baseline assessment, 67 patients with stable CHF were randomized to receive Q-ter 320 mg + creatine 340 mg (n = 35) or placebo (n = 32) once daily for 8 weeks.

At multivariate analysis, 8-week peak VO_2 was significantly higher in the active treatment group than in the placebo group (+1.8 ± 0.9

mL/min/kg, 95% CI: 0.1–3.6, $P < 0.05$). No untoward effects occurred in either group.

This study suggests that oral Q-ter and creatine, added to conventional drug therapy, exert some beneficial effect on physical performance in stable systolic CHF. Results may support the design of larger studies aimed at assessing the long-term effects of this treatment on functional status and harder outcomes. © 2011 Wiley Periodicals, Inc.[121]

Coenzyme Q10 Plus NADH Supplementation Improves Fatigue and Health-Related Quality of Life in Individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex, multisystem, and profoundly debilitating neuroimmune disease, probably of post-viral multifactorial etiology. Unfortunately, no accurate diagnostic or laboratory tests have been established, nor are any universally effective approved drugs currently available for its treatment. This study aimed to examine whether oral coenzyme Q10 and NADH (reduced form of nicotinamide adenine dinucleotide) co-supplementation could improve perceived fatigue, unrefreshing sleep, and health-related quality of life in ME/CFS patients. A 12-week prospective, randomized, double-blind, placebo-controlled trial was conducted in 207 patients with ME/CFS, who were randomly allocated to one of two groups to receive either 200 mg of CoQ10 and 20 mg of NADH (n = 104) or matching placebo (n = 103) once daily. Endpoints were simultaneously evaluated at baseline, and then reassessed at 4- and 8-week treatment visits and four weeks after treatment cessation, using validated patient-reported outcome measures. A significant

reduction in cognitive fatigue perception and overall FIS-40 score ($p < 0.001$ and $p = 0.022$, respectively) and an improvement in HRQoL (health-related quality of life (SF-36)) ($p < 0.05$) from baseline were observed within the experimental group over time. Statistically significant differences were also shown for sleep duration at 4 weeks and habitual sleep efficiency at 8 weeks in follow-up visits from baseline within the experimental group ($p = 0.018$ and $p = 0.038$, respectively). Overall, these findings support the use of CoQ10 plus NADH supplementation as a potentially safe therapeutic option for reducing perceived cognitive fatigue and improving the health-related quality of life in ME/CFS patients. Future interventions are needed to corroborate these clinical benefits and also explore the underlying pathomechanisms of CoQ10 and NADH administration in ME/CFS.[117]

Coenzyme Q10 improves tinnitus severity and sleep quality in patients with presbycusis

Introduction: Tinnitus is one of the symptoms of presbycusis that affects patients' sleep and social life. This study aimed to determine the effect of coenzyme Q10 (CoQ10) on treating tinnitus due to presbycusis.

Materials and methods: In this double-blind, randomized clinical trial, 50 patients with tinnitus due to presbycusis were randomly divided into groups A and B, with 25 patients in each group. In addition to routine treatments, group A received 100 mg of CoQ10 daily, while group B received a placebo. Both groups were evaluated for tinnitus severity, loudness of tinnitus, quality of life, and sleep disturbance before and 6 weeks after starting the treatment.

Results: In the intervention and control groups, the mean changes in score compared to before the treatment were as follows: quality of life

(3.1 ± 1.67) and (1.28 ± 0.76) (P = 0.298), sleep disorder (-7.60 ± 1.38) and (-1.0 ± 8.55) (P<0.001), tinnitus disability (-17.2 ± 52.93) and (-4.56 ± 1.37) (P<0.001), tinnitus loudness of right ear (-1.68 ± 0.41) and (-0.95 ± 0.23) (P=0.11) and left ear (-2.2 ± 0.35) and (-0.54 ± 0.21) (P<0.001).

Conclusion: This study indicated that adding CoQ10 to the routine regimen for patients with tinnitus due to presbycusis significantly decreases tinnitus disability, improves sleep disturbance, and reduces tinnitus loudness.[120]

Hypertension

Another important cardiovascular risk factor that CoQ10 may impact is elevated blood pressure. An early clinical study showed that doses as low as 30 mg per day could lower blood pressure.[20] A larger, double-blind, cross-over study involving 18 patients confirmed the effectiveness of CoQ10 for hypertension.[21] After stopping all antihypertensive drugs, hypertensive subjects showed a significant drop in systolic and diastolic blood pressure when taking 100 mg CoQ10 per day compared to placebo. Usually three to four weeks of treatment were necessary before blood pressures started to decrease. There were no adverse reactions.

In another more recent study, 109 patients with essential hypertension were supplemented with CoQ10 at an average oral dose of 225 mg/day in addition to their existing antihypertensive drug regimen. Eighty percent of patients in the study had been diagnosed with hypertension for an average of 9.2 years. Dosage was dependent on blood levels of CoQ10, the objective being to maintain blood levels of greater than 2.0 mcg/mL. Patients were gradually able to decrease antihypertensive drug therapy during the first one to six months. Fifty-one percent of patients were able to completely discontinue between

one and three antihypertensive drugs an average of 4.4 months after starting CoQ10. [22]

It is not entirely clear how CoQ10 lowers blood pressure. Many hypertensive persons have a deficiency of CoQ10.[21, 23] CoQ10 also tends to inhibit the synthesis of aldosterone, the hormone responsible for water retention and blood pressure elevation in vitro. [24]

Adjunctive to patients undergoing Heart Surgery

Patients who undergo heart surgery may develop CoQ10 deficiency. One study in patients undergoing valve replacement showed that supplementation of CoQ10 prevented low cardiac output far more than placebo.[25] The dose in this study was 30-60 mg daily of CoQ10 six days preoperatively. CoQ10-treated patients required less medication after surgery compared to controls.

Another study looked at patients primarily undergoing coronary artery bypass surgery.[26] Twenty patients took either 100 mg CoQ10 daily or placebo. Therapy was initiated 14 days pre-surgically and continued for 30 days after. Measures of heart function including ejection fraction as well as the course of recovery were significantly better in patients treated with CoQ10 than those in the control group. Preoperative deficiencies of CoQ10 were corrected by supplementation but not by placebo. Finally, heart transplantation usually leads to deficiencies of CoQ10 as well as vitamin E.[27] Worsening degrees of deficiency were correlated more closely with rejection.

Another important cause of CoQ10 deficiency is administration of HMG-CoA reductase cholesterol lowering drugs, which include lovastatin (Mevacor), pravastatin (Pravachol) and simvastatin (Zocor).[28, 29, 30] The same enzyme, HMG-CoA reductase, that starts the process of cholesterol synthesis is also responsible for CoQ10

synthesis. It is unclear what clinical relevance these findings have. One study found that LDL was more readily oxidized in patients treated with lovastatin.[31] This was partially due to a decline in CoQ10 levels in LDL. Long-term use of HMG-CoA reductase inhibitors has not been shown to have a negative effect on the cardiovascular system despite this anti-CoQ10 effect. It may nevertheless be advisable for patients taking these drugs to supplement CoQ10.

According to Emile G. Bliznakov, MD a CoQ10 researcher for decades, ” Two U.S. patents were granted to Merck(Pharmaceutical Company) in 1990 describing a method for counteracting the statin-associated myopathy and potential nerve damage caused by statins. The method described was the addition of CoQ10 to compensate for the reduced production of CoQ-10 caused by the statins. Thus the manufacturer itself implicated the serious side effects of statins and the protective role played by CoQ-10 in preventing these statin side-effects. The manufacturer has not disseminated these data for 12 years, which incriminates them seriously.” [56]

Statins’ effect on plasma levels of Coenzyme Q10 and improvement in myopathy with supplementation.

PURPOSE:

Heart disease is the leading cause of death in the United States. HMG-CoA reductase inhibitors, or statins, are medications at the forefront of the battle against cardiovascular disease. Despite their effectiveness, patient compliance with statins has lagged because of medication cost and adverse effects, namely myopathy. Myopathy is the most common side effect of statin use. The purpose of this review is to report plasma levels of CoQ10 in patients taking statins and then to determine the benefit of Coenzyme Q10 (CoQ10) supplementation on statin-related

myopathy as evidenced by symptomatic improvement and increase in serum levels of CoQ10.

DATA SOURCES:

CINAHL, Medline, Health Source: Nursing/Academic Edition, and Cochrane Library.

CONCLUSIONS:

Evidence from this review suggests that studies showed a significant relationship between statin intake and decreased serum levels of CoQ10. A few studies showed a benefit in symptoms of myalgia or improvement of serum levels of CoQ10 with supplementation. One study showed no benefit of CoQ10 supplementation when taken with statins. There were no risks of supplementation reported in any of the studies.

IMPLICATIONS FOR PRACTICE:

CoQ10 supplementation might benefit those patients suffering from statin-induced myopathy as evidenced by the results of these studies. Supplementation of CoQ10 at a dose of between 30 and 200 mg daily has shown to have beneficial effects on statin myopathy with no noted side effects. Further research is necessary.[88]

Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials.

OBJECTIVE:

To evaluate the efficacy of coenzyme Q10 (CoQ10) supplementation on statin-induced myopathy.

PARTICIPANTS AND METHODS:

We searched the MEDLINE, Cochrane Library, Scopus, and EMBASE databases (November 1, 1987, to May 1, 2014) to identify randomized controlled trials investigating the impact of CoQ10 on muscle pain and plasma creatine kinase (CK) activity as 2 measures of statin-induced myalgia. Two independent reviewers extracted data on study characteristics, methods, and outcomes.

RESULTS:

We included 6 studies with 302 patients receiving statin therapy: 5 studies with 226 participants evaluated the effect of CoQ10 supplementation on plasma CK activity, and 5 studies (4 used in the CK analysis and 1 other study) with 253 participants were included to assess the effect of CoQ10 supplementation on muscle pain. Compared with the control group, plasma CK activity was increased after CoQ10 supplementation, but this change was not significant (mean difference, 11.69 U/L [to convert to μkat/L, multiply by 0.0167]; 95% CI, -14.25 to 37.63 U/L; P=.38). Likewise, CoQ10 supplementation had no significant effect on muscle pain despite a trend toward a decrease (standardized mean difference, -0.53; 95% CI, -1.33 to 0.28; P=.20). No dose-effect association between changes in plasma CK activity (slope, -0.001; 95% CI, -0.004 to 0.001; P=.33) or in the indices of muscle pain (slope, 0.002; 95% CI, -0.005 to 0.010; P=.67) and administered doses of CoQ10 were observed.

CONCLUSION:

The results of this meta-analysis of available randomized controlled trials do not suggest any significant benefit of CoQ10 supplementation in improving statin-induced myopathy. Larger, well-designed trials are necessary to confirm the findings from this meta-analysis.[90]

CoQ10 supplementation ameliorated statin-associated myopathy: An Updated Meta-Analysis of Randomized Controlled Trials

Background Previous studies have demonstrated a possible association between the induction of coenzyme Q10 (CoQ10) after statin treatment and statin-induced myopathy. However, whether CoQ10 supplementation ameliorates statin-induced myopathy remains unclear. Methods and Results PubMed, EMBASE , and Cochrane Library were searched to identify randomized controlled trials investigating the effect of CoQ10 on statin-induced myopathy. We calculated the pooled weighted mean difference (WMD) using a fixed-effect model and a random-effect model to assess the effects of CoQ10supplementation on statin-associated muscle symptoms and plasma creatine kinase. The methodological quality of the studies was determined, according to the Cochrane Handbook. Publication bias was evaluated by a funnel plot, Egger regression test, and the Begg-Mazumdar correlation test. Twelve randomized controlled trials with a total of 575 patients were enrolled; of them, 294 patients were in the CoQ10 supplementation group and 281 were in the placebo group. Compared with placebo, CoQ10 supplementation ameliorated statin-associated muscle symptoms, such as muscle pain (WMD , -1.60; 95% confidence interval [CI], -1.75 to -1.44; P<0.001), muscle weakness (WMD , -2.28; 95% CI , -2.79 to -1.77; P=0.006), muscle cramp (WMD , -1.78; 95% CI , -2.31 to -1.24; P<0.001), and muscle tiredness (WMD , -1.75; 95% CI , -2.31 to -1.19; P<0.001), whereas no reduction in the plasma creatine kinase level was observed after CoQ10supplementation (WMD , 0.09; 95% CI , -0.06 to 0.24; P=0.23).

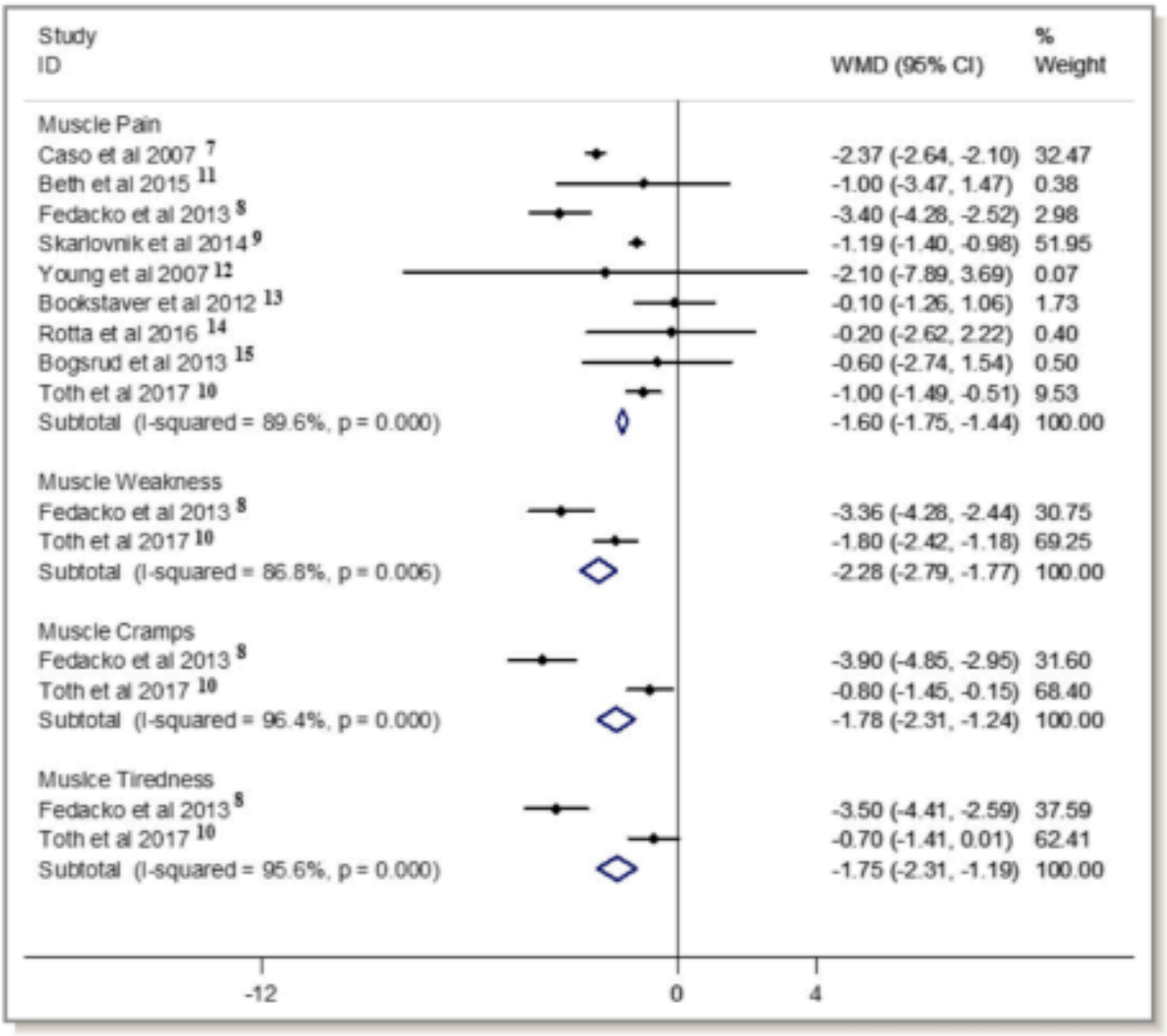


Figure 3. Forest plot for statin-associated muscle symptoms: coenzyme Q10 vs placebo (fixed-effect model). CI indicates confidence interval; ID, identification; WMD, weighted mean difference.

Conclusions CoQ10 supplementation ameliorated statin-associated muscle symptoms, implying that CoQ10 supplementation may be a complementary approach to manage statin-induced myopathy.[98]

Boost heart health of diabetics on statins

Co Q10 increased the vascular health of diabetics on statins, according to a new study from Australia. “Following 12 weeks of supplementation with CoQ10 (200mg per day) an improvement in the blood flow was observed, according to findings published in the journal *Diabetes Care*.” *“The patients in our study had endothelial dysfunction despite satisfactory control of blood pressure, glycemic and lipids, which may*

represent the proportion of statin-treated patients at increased residual risk of cardiovascular disease," wrote the researchers, led by Professor Gerald Watts from the University of Western Australia. *"Our absolute improvement in [blood flow in the arm] of 1 per cent with CoQ10 supplementation may potentially translate to a 10-25 per cent reduction in residual cardiovascular risk in these patients."* [81]

Selenium and Coenzyme Q_{10} Decreased Concentration of FGF-23, Cardiovascular Disease in an Elderly Swedish Population

There is a reduced intake of selenium in many countries due to low levels of selenium in the soil. This results in an increased cardiovascular risk. Fibroblast growth factor 23 (FGF-23) is active mainly in the metabolism of vitamin D and phosphorus. However, there are indications that FGF-23 may also provide information both on cardiovascular function and prognosis. The aim of the study was to evaluate the effect of supplementation with selenium and coenzyme Q_{10} on the FGF-23 concentration in an elderly population with low concentrations of both selenium and coenzyme Q_{10} and in which the supplementation improved cardiac function and mortality. In a randomized double-blind placebo-controlled trial, FGF-23 was measured in 219 individuals at the start and after 48 months. Selenium yeast (200 µg/day) and coenzyme Q_{10} (200 mg/day) (n = 118) or placebo (n = 101) were given as a dietary supplement. The intervention time was 48 months. t-Tests, repeated measures of variance, and ANCOVA analyses were used to evaluate the differences in FGF-23 concentration. Following supplementation with selenium and coenzyme Q_{10}, a significantly lower level of FGF-23 could be seen (p = 0.01). Applying 10 years of follow-up, those who later died a cardiovascular death had a significantly higher FGF-23 concentration after 48 months compared with those who survived (p = 0.036), and a significantly

lower FGF-23 concentration could be seen in those with a normal renal function compared to those with an impaired renal function (p = 0.027). Supplementation with selenium and coenzyme Q_{10} to an elderly community-living population low in both substances prevented an increase of FGF-23 and also provided a reduced cardiovascular risk.[109]

Mitochondrial efficiency enhancement

Six patients with different mitochondrial cytopathies were studied. Before CoQ10 we found a low phosphocreatine content (average of 25% decrease from controls) in the occipital lobes of all patients. Calculated [ADP] and the relative rate of ATP synthesis were high (as an average, 57% and 16% above control group respectively), whereas the cytosolic phosphorylation potential was low (as an average, 60% of control value). 31P-MRS also revealed an average of 29% reduction of the mitochondrial function in the skeletal muscle of patients compared with controls. After a six-month treatment with 150 mg CoQ10/day all brain variables were remarkably improved in all patients, returning within the control range in all cases. Treatment with CoQ10 also improved the muscle mitochondrial functionality enough to reduce the average deficit to 56% of the control group. These in vivo findings show the beneficial effect of CoQ10 in patients with mitochondrial cytopathies, and are consistent with the view that increased CoQ10 concentration in the mitochondrial membrane increases the efficiency of oxidative phosphorylation independently of enzyme deficit. [48]

Anti-atherogenic

CoQ10 has a direct anti-atherogenic effect, which has been demonstrated in apolipoprotein E-deficient mice fed with a high-fat diet. In this model, supplementation with CoQ10 at pharmacological doses was capable of decreasing the absolute concentration of lipid

hydroperoxides in atherosclerotic lesions and of minimizing the size of atherosclerotic lesions in the whole aorta. [83]

Effect of coenzyme q10 on the incidence of atrial fibrillation in patients with heart failure.

BACKGROUND:

There is mounting evidence to support the influence of inflammation and oxidative stress in the pathogenesis of atrial fibrillation (AF) and heart failure (HF). The efficacy of coenzymeQ10 (CoQ10), an antioxidant used as an adjunct treatment in patients with AF and HF, remains less well established.

METHODS:

Consecutive patients with HF were randomized and divided into 2 groups: the CoQ10 group (combined administration of common drugs and CoQ10) and the control group (administration of common drugs). Ambulatory electrocardiogram Holter monitoring (24 hours), Doppler echocardiography, and evaluation of inflammatory cytokines were performed before treatment and 6 and 12 months after treatment.

RESULTS:

One hundred two patients (72 male and 30 female patients), with ages ranging from 45 to 82 years (mean age, 62.3 years), were examined. There was significant reduction in the level of malondialdehyde (3.9 ± 0.7 vs 2.5 ± 0.6 ng/mL; 3.9 ± 0.7 vs 2.3 ± 0.5 ng/mL, $P < 0.05$) in the CoQ10 group, whereas there was no significant difference (3.3 ± 0.8 vs 2.9 ± 0.8 ng/mL; 3.3 ± 0.8 vs 2.9 ± 0.5 ng/mL) in the control group after 6 and 12 months. Three patients (6.3%) in the CoQ10 group and 12 patients (22.2%) in the control group had episodes of AF after 12

months' treatment (P = 0.02). Four patients with AF in the control group went through the third Holter recording.

CONCLUSIONS:

CoenzymeQ10 as adjuvant treatment in patients with HF may attenuate the incidence of AF. The mechanisms of the effect perhaps have relation with the reduced levels of malondialdehyde.[89]

Coenzyme Q10 improves nitric oxide - related dilation of the rat aorta

This study examined whether coenzyme Q10 can improve nitric oxide (NO)-dependent vasodilatation in the rat aorta after pre-incubation or intravenous administration. In initial experiments, intact isolated aortic rings were incubated with coenzyme Q10 or L-arginine. In further experiments, coenzyme Q10 was administered intravenously in anesthetized rats, then in 2 h aorta was isolated. In both cases, after preliminary preparation the isolated aortic rings were tested for acetylcholine-induced NO-dependent relaxation. Acetylcholine elicited concentration-dependent relaxation of phenylephine precontracted aortic rings. Relaxant responses to acetylcholine were markedly potentiated after pre-incubation with coenzyme Q10 or L-arginine. The maximum relaxant responses (%) were significantly increased from 64.1±5.3 (control) to 89.8±3.0 and 83.6±3.0 (coenzyme Q10 and L-arginine, respectively). pD2 (-lgEC50) value in control study was 5.81±0.28, after pretreatment with coenzyme Q10 or L-arginine were 7.59 ± 0.16 and 7.26 ± 0.32, respectively. There was no difference between coenzyme Q10 and L-arginine groups. After intravenous administration, the relaxant responses to acetylcholine were significantly increased in coenzyme Q10-treated group (94.2 ± 2.0) compared with controls (68.1 ± 4.4). pD2 values were also different

between control and treatment groups (5.79 ± 0.29 vs. 8.14 ± 0.65, respectively).

Thus, coenzyme Q10 improved NO-mediated vasodilation in rat aorta in magnitude close to the effects of L- arginine – substrate for eNOS. Our data first show that exogenous coenzyme Q10 through intravenous administration is able to improve rapidly NO-dependent vasodilation in rat aorta, likely due to accumulation of coenzyme Q10 in the vessel wall. Improvement of endothelial function can contribute, at least in part, to beneficial effects of coenzyme Q10 in cardiovascular diseases associated with endothelial dysfunction.[94]

Coenzyme Q10 supplementation reduces inflammatory markers: A systematic review and meta-analysis of randomized controlled trials

The aims of this meta-analysis were to evaluate the effects of coenzyme Q10 (CoQ10) supplementation on inflammatory mediators including C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) by analyzing published randomized controlled trials (RCTs). A systematic search in PubMed, Cochrane Library and Clinicaltrials.gov was performed to identify eligible RCTs. Data synthesis was performed using a random- or a fixed-effects model depending on the results of heterogeneity tests, and pooled data were displayed as weighed mean difference (WMD) and 95% confidence interval (CI). Seventeen RCTs were selected for the meta-analysis. CoQ10 supplementation significantly reduced the levels of circulating CRP (WMD: −0.35 mg/L, 95% CI: −0.64 to −0.05, P = 0.022), IL-6 (WMD: −1.61 pg/mL, 95% CI: −2.64 to −0.58, P = 0.002) and TNF-α (WMD: −0.49 pg/mL, 95% CI: −0.93 to −0.06, P = 0.027). The results of meta-regression showed that the changes of

CRP were independent of baseline CRP, treatment duration, dosage, and patients characteristics. In the meta-regression analyses, a higher baseline IL-6 level was significantly associated with greater effects of CoQ10 on IL-6 levels (*P* for interaction = 0.006). In conclusion, this meta-analysis of RCTs suggests significant lowering effects of CoQ10 on CRP, IL-6 and TNF-α. However, results should be interpreted with caution because of the evidence of heterogeneity and limited number of studies.[97]

Increases brain mitochondrial concentrations and neuroprotective

Feeding with CoQ10 increased cerebral cortex concentrations in 12- and 24-month-old rats. In 12-month-old rats administration of CoQ10 resulted in significant increases in cerebral cortex mitochondrial concentrations of CoQ10. Oral administration of coenzyme Q10 markedly attenuated striatal lesions produced by systemic administration of 3-nitropropionic acid and significantly increased life span in a transgenic mouse model of familial amyotrophic lateral sclerosis. These results show that oral administration of CoQ10increases both brain and brain mitochondrial concentrations. They provide further evidence that CoQ10 can exert neuroprotective effects that might be useful in the treatment of neurodegenerative diseases. [49]

Coenzyme Q10 deficiency can be expected to compromise Sirt1 activity

When CoQ10 levels are sufficiently low, this compromises the efficiency of the mitochondrial electron transport chain, such that production of superoxide by site 2 increases and the rate of adenosine triphosphate production declines. Moreover, CoQ10 deficiency can be expected to decrease activities of Sirt1 and Sirt3 deacetylases, believed to be key determinants of health span. Reduction of the

cytoplasmic and mitochondrial NAD^+/NADH ratio consequent to CoQ10 deficit can be expected to decrease the activity of these deacetylases by lessening availability of their obligate substrate NAD^+ The increased oxidant production induced by CoQ10 deficiency can decrease the stability of Sirt1 protein by complementary mechanisms. And CoQ10 deficiency has also been found to lower mRNA expression of Sirt1. An analysis of the roles of Sirt1/Sirt3 in modulation of cellular function helps to rationalize clinical benefits of CoQ10 supplementation reported in heart failure, hypertension, non-alcoholic fatty liver disease, metabolic syndrome and periodontal disease. Hence, correction of CoQ10 deficiency joins a growing list of measures that have potential for amplifying health protective Sirt1/Sirt3 activities.[110]

Inhibits brain cell damage, improves learning and memory

Although the mechanism of Alzheimer's is not clear, more support is gathering for the build-up of plaque from amyloid deposits. The deposits are associated with an increase in brain cell damage and death from oxidative stress. CoQ10 improves learning and memory deficits possibly by inhibiting the oxidative stress and improving levels of ATP. [69]

Serum coenzyme Q10 and risk of disabling dementia: the Circulatory Risk in Communities Study (CIRCS).

OBJECTIVE:

To examine whether coenzyme Q10, a potent antioxidant, is associated with risk of dementia, which has not yet been elucidated.

APPROACH AND RESULTS:

We performed a case-control study nested in a community-based cohort of approximately 6000 Japanese aged 40-69 years at baseline

(1984-1994). Serum coenzyme Q10 was measured in 65 incident cases of disabling dementia with dementia-related behavioral disturbance or cognitive impairment incident between 1999 and 2004, and in 130 age-, sex- and baseline year-matched controls. Serum coenzyme Q10 was inversely associated with dementia: the multivariate odds ratios (95% confidence intervals) were 0.68 (0.26-1.78), 0.92 (0.33-2.56), and 0.23 (0.06-0.86) for individuals with the second, third, and highest quartiles of coenzyme Q10, respectively, as compared with the lowest quartile (P for trend = 0.05). A similar association was found for the coenzyme Q10/total cholesterol ratio: the respective ORs were 0.67 (0.25-1.78), 0.73 (0.28-1.92), and 0.21 (0.05-0.90) (P for trend = 0.04).

CONCLUSIONS:

Serum coenzyme Q10 levels were inversely associated with risk of disabling dementia.[91]

Vinpocetine and coenzyme Q10 combination alleviates cognitive impairment caused by ionizing radiation by improving mitophagy

Objective: This research was designed to ascertain the effect and mechanism of vinpocetine (VIN) and coenzyme Q10 (CoQ10) combination on cognitive impairment induced by ionizing radiation (IR).

Methods: Cognitive impairment in mice was induced by 9-Gy IR, and they were intraperitoneally injected with VIN, CoQ10, or VIN + CoQ10. Then novel object recognition and Morris water maze tests were used to detect cognitive function. The number of hippocampal neurons and $BrdU^{+}Dcx^{+}$ cells was observed by Nissl and immunofluorescence staining. Mitochondrial respiratory complex I, adenosine triphosphate (ATP), and mitochondrial membrane potential (MMP) were evaluated, as well as oxidative stress injury. Mitophagy in hippocampal neurons

was evaluated by observing the ultrastructure of hippocampal neurons and assessing the expression of mitophagy-related proteins.

Results: IR reduced novel object discrimination index, the time for platform crossing, and the time spent in platform quadrant, in addition to neuron loss, downregulated levels of mitochondrial respiratory complex I, ATP, and MMP, aggravated oxidative stress injury, increased expression of LC3 II/I, Beclin1, PINK1, and parkin, and decreased P62 expression. VIN or CoQ10 treatment mitigated cognitive dysfunction, neurons loss, mitochondrial damage, and oxidative stress injury, and enhanced mitophagy in hippocampal neurons. VIN and CoQ10 combination further protected against IR-induced cognitive dysfunction than VIN or CoQ10 alone.

Conclusion: VIN combined with CoQ10 improved neuron damage, promoted mitophagy, and ameliorated cognitive impairment in IR mice.[111]

Mitochondrial encephalomyopathy

There is one published report of human CoQ10 deficiency describing two sisters with encephalopathy, proximal weakness, myoglobinuria and lactic acidosis. We report a patient who had delayed motor milestones, proximal weakness, premature exertional fatigue and episodes of exercise-induced pigmenturia. She also developed partial-complex seizures. Serum creatine kinase was approximately four times the upper limit of normal and venous lactate was mildly elevated. Skeletal muscle biopsy revealed many ragged-red fibers, cytochrome c oxidase-deficient fibers and excess lipid. In isolated muscle mitochondria, impaired oxygen consumption was corrected by the addition of decylubiquinone. During standardized exercise, ventilatory and circulatory responses were compatible with a defect of oxidation-phosphorylation, which was confirmed by near-infrared spectroscopy analysis. Biochemical analysis of muscle extracts revealed decreased

activities of complexes I+II and I+III, while CoQ10 concentration was less than 25% of normal. With a brief course of CoQ10 (150 mg daily), the patient reported subjective improvement. CO Q supplementation should be strongly considered in the treatment of encephalopathy. [50]

Effect of coenzyme Q10 supplementation on fatigue: A systematic review of interventional studies.

AIMS:

A number of studies have examined the beneficial effects of Coenzyme Q10 (CoQ10) on fatigue in different population, but the findings have been inconclusive. Herein, we systematically reviewed available interventional studies to elucidate the overall effects of CoQ10 supplementation on fatigue among adolescent and adult population.

METHODS:

PubMed, Cochrane's library, Science direct, Scopus, Google scholar and ISI web of science databases were searched for all available literature until April 2018 for studies assessing the effects of CoQ10 supplementation on fatigue. The Cochrane bias assessment tool were used to assess the quality of studies.

RESULTS:

A total of 16 studies out of 1316 met our inclusion criteria and included in our systematic review. Among included studies 10 of them showed significant beneficial effects ($p < 0.05$) of CoQ10 supplementation on fatigue status among healthy, fibromyalgia, statin-related fatigue, multiple sclerosis and end-stage heart failure subjects.[99]

Reduction in Oxidative stress, and improvement in arterial tone

Age-associated deterioration of arterial function may result from long-lasting oxidative stress. Since CoQ10 has been suggested to protect the vascular endothelium from free radical-induced damage, a study was conducted to monitor the effects of long-term dietary Q10 supplementation on arterial function in senescent Wistar rats. 2. At 16 months of age, 18 rats were divided into two groups. The control group was kept on a standard diet while the other group was supplemented with Q10 (10 mg kg(-1) day(-1)). In addition, nine rats (age 2 months) also ingesting a standard diet were used as the young control group. After 8 study weeks the responses of the mesenteric arterial rings in vitro were examined. 3. In conclusion of the study, long-term Q10 supplementation improved endothelium-dependent vasodilation and enhanced beta-adrenoceptor-mediated arterial relaxation in senescent Wistar rats. The mechanisms underlying the improvement of endothelial function may have included augmented endothelial production of PGI2, increased sensitivity of smooth muscle to PGI2 or both. [51]

Prevention of ischemic brain lesions

In CoQ10-untreated rabbits, moderate to severe neurological deficits developed, and multiple focal ischemic lesions were found in the brain regions with compromised blood supply, i.e., in the regions normally supplied by common carotid arteries which are subject to ligation in this model. CoQ10 treatment prevented the development of both the neurological deficits and histologically detectable brain tissue damage. [52]

Parkinson’s disease.

A defect in mitochondrial oxidative phosphorylation, in terms of a reduction in the activity of NADH CoQ reductase (complex I) has been reported in the striatum of patients with Parkinson's disease. The reduction in the activity of complex I is found in the substantia nigra, but not in other areas of the brain, such as globus pallidus or cerebral cortex. Therefore, the specificity of mitochondrial impairment may play a role in the degeneration of nigrostriatal dopaminergic neurons.. Although the serum levels of CoQ10 is normal in patients with Parkinson's disease, CoQ10 is able to attenuate the MPTP-induced loss of striatal dopaminergic neurons. [53]

A national clinical trial with 80 Parkinson's disease patients has shown that high dosages of a naturally occurring compound, CoQ10, slowed by 44 percent the progressive deterioration in function that occurs in the disease. The greatest benefit was seen in everyday activities such as feeding, dressing, bathing and walking. [54]

The most useful treatment for the prevention and treatment of neurodegenerative diseases including Parkinson's include supplemental creatine (Amino Max and Beyond Whey), coenzyme Q10, with phenolic compounds, such as Green tea extract (Botanical Treasures and Thermo-Fit) and recently peroxisome proliferator-activated receptor-gamma-coactivators, such as Grape seed extract (CV-RES-Q and Botanical Treasures) and sirtuins (CV-RES-Q), provide great promise for future therapeutic developments in neurodegenerative disorders.[79]

Muscular dystrophies and neurogenic atrophies.

The first of two double-blind trials involved twelve patients, ranging from 7 to 69 years of age, having diseases including the Duchenne, Becker, and the limb-girdle dystrophies, myotonic dystrophy. Charcot-

Marie-Tooth disease, and the Welander disease. The control coenzyme Q10 (CoQ10) blood level was low and ranged from 0.5 to 0.84 microgram/ml. They were treated for three months with 100 mg daily of CoQ10 and a matching placebo. The second double-blind trial was similar with fifteen patients having the same categories of disease. Since cardiac disease is established to be associated with these muscle diseases, cardiac function was blindly monitored, and not one mistake was made in assigning CoQ10 and placebo to the patients in both trials. Definitely improved physical performance was recorded. In retrospect, a dosage of 100 mg was too low although effective and safe. Patients suffering from these muscle dystrophies and the like, should be treated with vitamin Q10 indefinitely. [55]

Prevention of mitochondrial toxin-induced injury

Mitochondrial toxins produce striatal excitotoxic lesions by a mechanism involving energy depletion. Both CoQ10 and nicotinamide (co enzyme of vitamin B-3) blocked adenosine triphosphate depletions and producing neuroprotective effect.[56]

Coenzyme Q10 supplementation reduces oxidative s enzyme activity in patients with coronary artery disease.

The purpose of this study was to investigate the effect of conzyme Q10 supplementation on oxidative stress and antioxidant enzyme activity in patients with coronary artery disease (CAD).

This was an intervention study. Patients who were identified by cardiac catheterization as having at least 50% stenosis of one major coronary artery or receiving percutaneous transluminal coronary angioplasty (n = 51) were randomly assigned to

the placebo group (n = 14) or one of the two coenzyme Q10-supplemented groups (60 mg/d, n = 19 [Q10-60 group]; 150 mg/d, n = 18 [Q10-150 group]). Intervention was administered for 12 wk. Patients' blood samples were analyzed every 4 wk for plasma coenzyme Q10 concentrations, malondialdehyde (MDA), and antioxidant enzyme (catalase [CAT], superoxide dismutase [SOD], glutathione peroxidase) activity.

Forty-three subjects with CAD completed intervention study. Plasma coenzyme Q10 concentration increased significantly after coenzyme the Q10-150 intervention ($P < 0.01$). The MDA levels were significantly lower than baseline in the Q10-150 group at week 4 ($P = 0.03$). The Q10-150 group had significantly lower MDA levels than the placebo group at week 8 ($P = 0.03$). With respect to antioxidant enzyme activity, subjects in the Q10-150 group had significantly higher CAT ($P = 0.03$) and SOD ($P = 0.03$) activity than the placebo group at week 12. The plasma coenzyme Q10 concentration was significantly correlated with MDA levels ($r = -0.35$, $P = 0.02$) and CAT ($r = 0.43$, $P = 0.01$) and SOD activity ($r = 0.39$, $P = 0.01$). The ratio of plasma coenzyme Q10 to total cholesterol was significantly correlated with SOD activity ($r = 0.39$, $P = 0.02$). The ratio of plasma coenzyme Q10 to low-density lipoprotein was significantly correlated with CAT ($r = 0.35$, $P = 0.04$) and SOD ($r = 0.45$, $P = 0.01$) activity. However, there was no relation between coenzyme Q10 concentration and glutathione peroxidase activity.

CONCLUSION:

Coenzyme Q10 supplements at a dose of 150 mg can decrease oxidative stress and increase antioxidant enzyme activity in patients with CAD. A higher

dose of coenzyme Q10 supplements (>150 mg/d) might promote rapid and sustainable antioxidation in patients with CAD.[95]

Selenium and coenzyme Q10 for four years reduced cardiovascular mortality 12 years after supplementation with: A validation of previous 10-year follow-up results of a prospective randomized double-blind placebo-controlled trial in elderly

Selenium and coenzyme Q10 are both necessary for optimal cell function in the body. The intake of selenium is low in Europe, and the endogenous production of coenzyme Q10 decreases as age increases. Therefore, an intervention trial using selenium and coenzyme Q10 for four years as a dietary supplement was performed. The main publication reported reduced cardiovascular mortality as a result of the intervention. In the present sub-study the objective was to determine whether reduced cardiovascular (CV) mortality persisted after 12 years, in the supplemented population or in subgroups with diabetes, hypertension, ischemic heart disease or reduced functional capacity due to impaired cardiac function.

From a rural municipality in Sweden, four hundred forty-three healthy elderly individuals were included. All cardiovascular mortality was registered, and no participant was lost to the follow-up. Based on death certificates and autopsy results, mortality was registered. Findings After 12 years a significantly reduced CV mortality could be seen in those supplemented with selenium and coenzyme Q10, with a CV mortality of 28.1% in the active treatment group, and 38.7% in the placebo group. A multivariate Cox regression analysis demonstrated a reduced CV mortality risk in the active treatment group (HR: 0.59; 95%CI 0.42–0.81; P = 0.001). In those with ischemic heart disease, diabetes, hypertension and impaired functional capacity we demonstrated a significantly reduced CV mortality risk.

Conclusions This is a 12-year follow-up of a group of healthy elderly participants that were supplemented with selenium and coenzyme Q10 for four years. **Even after twelve years we observed a 40% reduced risk for CV mortality in this group, as well as in subgroups of patients with diabetes, hypertension, ischemic heart disease or impaired functional capacity**. The results thus validate the results obtained in the 10-year evaluation. The protective action was not confined to the intervention period, but persisted during the follow-up period. The mechanisms behind this effect remain to be fully elucidated, although various effects on cardiac function, oxidative stress, fibrosis and inflammation have previously been identified. Since this was a small study, the observations should be regarded as hypothesis-generating.[96]

Chemotherapy and Cancer

CoQ 10 being a vital constituent of the mitochondrial electron transport function also makes this super nutrient an important agent in nutritional oncology. One critical area in which CoQ10 is a specific for is to protect the heart during chemotherapy in particular doxorubicin (Adriamycin [ADM]). The major problem with this drug is its dose-dependent cardiotoxicity. Animal studies originally showed that CoQ10 administration could block the heart damage caused by doxorubicin.[32, 33. 61-64] Co Q10 strongly protected against the ADM-induced toxicity, and the mice administered CO Q10 lived significantly longer than the control mice. [62]

A preliminary study in 10 people being treated with Adriamycin, vincristine and cyclophosphamide found that 50 mg daily of CoQ10 was effective in reducing cardiotoxicity.[34] The bone marrow suppression caused by Adriamycin was not affected. There was no sign of interference with the effectiveness of the chemotherapeutic regime.

This study was designed to evaluate the usefulness of Coenzyme Q10 (CoQ10) in the prevention of side effects due to anthracycline agents-Adriamycin (ADM) and Daunorubicin (DNR)-by comparing the preventive effect between CoQ10-treated and non-treated groups. The subjects were 79 patients, 55 of whom had malignant lymphoma. The age range was from 16 to 77 years with a mean age of 45.4 years. CoQ10 was administered by intravenous drip at 1 mg/kg/day the day before ADM or DNR administration, on the day and for a further 2 days after administration. In mean total dose, complete remission rate and mortality, no significant differences were observed between the 2 groups. Although there were also no significant differences in the degree of alopecia, fever, nausea and vomiting, the incidences of diarrhea and stomatitis were significantly (p less than 0.10 and p less than 0.05, respectively) reduced in the CoQ10-treated group. Depression of ST waves (more than 0.05 mV) and changes in T waves (R/10 greater than T, flat, inversion) on ECG were regarded as a parameter of aggravation. Such ECG aggravation was found in 20 of 40 patients given CoQ10 (50.0%) and in 18 of 25 receiving none (72.0%); a cardiotoxicity-inhibiting tendency was thus evident (p less than 0.10). In heart rate, tachycardia was noted in the nontreated group when the period of use of anthracycline agents exceeded 8 weeks. Twenty nine patients received ADM or DNR for 8 weeks or more, and, of them, 17 were treated with CoQ10; 11 of the 17 (64.7%) showed EKG aggravation, while 11 of 12 patients (91.7%) not treated with CoQ10 showed EKG aggravation. A tendency to depress EKG aggravation was thus observed in the treated group (p less than 0.10). [63]

The effect of the association of carnitine and coenzyme Q10 on doxorubicin cardiotoxicity has been investigated. The two drugs administered to rats for two weeks have lower protective activity when they are administered separately rather than given in association (carnitine 200 mg/kg/day, coenzyme Q10 10 mg/kg/day) for the acute

toxic effect of doxorubicin on perfused functioning isolated hearts. Carnitine and coenzyme Q10 do not protect sarcoplasmic reticulum from iron ions damage, suggesting that their mechanism of protection is not directly related to peroxidation due to metal ion-dependent cardiotoxicity of doxorubicin. [61]

A recent study proved that Co Q10 does not interfere with the cytotoxic effects of chemo-drugs. [64]

Early, uncontrolled studies and case reports have suggested that CoQ10, alone or in combination with other nutrients, may benefit cancer patients. One study involved 32 breast cancer patients with lymph node metastasis undergoing allopathic treatment.[35] In a clinical protocol, 32 patients having high risk breast cancer were treated with antioxidants, fatty acids, and 90 mg of CoQ10. Six of the 32 patients showed tumor regression. In one of these six patients the dosage of CoQ10 was increased to 390 mg. In one month, that tumor was no longer palpable, and in another month, mammography confirmed the absence of the tumor. Encouraged, another case of verified breast cancer, after non-radical surgery and with verified residual tumor within the tumor bed, was then treated with 300 mg CoQ10. After three months, the patient was in excellent clinical condition and there was no residual tumor tissue. The bioenergetic activity of CoQ10, expressed as hematological or immunological activity, may be dominant but not the sole molecular mechanism causing the regression of breast cancer. [36]

Another study has documented that blood levels of CoQ10 are significantly lower in breast cancer and myeloma patients compared to healthy persons.[37] Mice that had been inoculated with cancer and treated with CoQ10 had more than double the lifespan of mice not given the CoQ10. [59] This further increases the possibility that CoQ10 might be beneficial as a supplement for people with cancer.

Enhanced antitumor efficacy and counterfeited cardiotoxicity of combinatorial oral therapy using Doxorubicin- and Coenzyme Q10-liquid crystalline nanoparticles in comparison with intravenous Adriamycin.

Present study focuses on enhancing oral antitumor efficacy and safety of Dox-LCNPs in combination with CoQ10-LCNPs. Drug-loaded-LCNPs were prepared by solvent-diffusion-evaporation method and optimized. Median effect analysis suggested dose-reduction-index of 16.84- and 5.047-fold and strong synergism for combination at 1:10 dose ratio owing to higher cellular uptake, nuclear colocalization, higher apoptotic index and 8-OHdG levels. The prophylactic antitumor efficacy of the CoQ10-LCNPs was also established using tumor induction and progression studies. Finally, therapeutic antitumor efficacy was found to be significantly higher (~1.76- and ~4.5-fold) for the combination as compared to Dox-LCNPs (per oral) and Adriamycin (i.v.) respectively. Notably, level of residual tumor burden was insignificant (P>0.05) after 30days in case of combination and LipoDox® (i.v.). Interestingly, with Dox-induced-cardiotoxicity was completely counterfeited in combination. In nutshell, LCNPs pose great potential in improving the therapeutic efficacy of drugs by oral route of administration.

FROM THE CLINICAL EDITOR:

This study describes the use of liquid crystalline nanoparticles containing coenzyme Q10 and doxorubicin. The nano-conjugates not only provided an enhanced oral treatment option for a tumor model, but

prevented cardiotoxicity, a major complication of this drug when delivered via conventional methods.[92]

Reverses mitochondrial dysfunction, fatigue and the adverse effects of chemotherapy of metastatic cancer patients

Metastatic cancers are associated with cellular oxidative stress, and during cancer chemotherapy excess drug-induced oxidative stress can limit therapeutic effectiveness and cause a number of side effects, including fatigue, nausea, vomiting, diarrhea and more serious adverse effects, such as cardiomyopathy, peripheral neuropathy, hepatotoxicity and pulmonary fibrosis. We review here the hypothesis that the acute and chronic adverse effects of cancer chemotherapy can be reduced by molecular replacement of membrane lipids and enzymatic cofactors, such as coenzyme Q(10). By administering nutritional supplements with replacement molecules and antioxidants, oxidative membrane damage and reductions of cofactors in normal tissues can be reversed, protecting and restoring mitochondrial and other cellular functions and reducing chemotherapy adverse effects. Recent clinical trials using cancer and non-cancer patients with chronic fatigue have shown the benefit of molecular replacement plus antioxidants in reducing the damage to mitochondrial membranes, restoring mitochondrial electron transport function, reducing fatigue and protecting cellular structures and enzymes from oxidative damage. Molecular replacement and antioxidant administration mitigates the damage to normal tissues, such as cardiac tissue, and reduces the adverse effects of cancer therapy without reduction in therapeutic results. [80]

Coenzyme Q10 Suppressed Invasion of Temozolomide-Resistant Rat Glioma *In Vitro* and *In Vivo*.

The main reasons for the inefficiency of standard glioblastoma (GBM) therapy are the occurrence of chemoresistance and the invasion of GBM cells into surrounding brain tissues. New therapeutic approaches obstructing these processes may provide substantial survival improvements. The purpose of this study was to assess the potential of lipophilic antioxidant coenzyme Q10 (CoQ10) as a scavenger of reactive oxygen species (ROS) to increase sensitivity to temozolomide (TMZ) and suppress glioma cell invasion. To that end, we used a previously established TMZ-resistant RC6 rat glioma cell line, characterized by increased production of ROS, altered antioxidative capacity, and high invasion potential.

- CoQ10 in combination with TMZ exerted a synergistic antiproliferative effect. These results were confirmed in a 3D model of microfluidic devices showing that the CoQ10 and TMZ combination is more cytotoxic to RC6 cells than TMZ monotherapy.
- In addition, cotreatment with TMZ increased expression of mitochondrial antioxidant enzymes in RC6 cells.
- The anti-invasive potential of the combined treatment was shown by gelatin degradation, Matrigel invasion, and 3D spheroid invasion assays as well as in animal models.
- Inhibition of MMP9 gene expression as well as decreased N-cadherin and vimentin protein expression implied that CoQ10 can suppress invasiveness and the epithelial to mesenchymal transition in RC6 cells.

Therefore, our data provide evidences in favor of CoQ10 supplementation to standard GBM treatment due to its potential to inhibit GBM invasion through modulation of the antioxidant capacity.[101]

Coenzyme Q10 Supplementation in Fibrosis and Aging

Coenzyme Q10 (CoQ10) is a vitamin-like substance which functions as an electron carrier within the mitochondrial respiratory chain, as well as serving as an important intracellular antioxidant. Most of the body's CoQ10 requirements are met by endogenous synthesis, although the capacity for CoQ10 production decreases substantially with increasing age. In this article we have reviewed the potential role of CoQ10 supplementation in the treatment of tissue fibrosis, which has been implicated in the age-related loss of function of various organs including the heart.

- Clinical studies have indicated that CoQ10 supplementation may decrease the level of cardiovascular fibrosis to which older individuals are subjected, and thereby improve cardiovascular function and reduce the risk of cardiovascular associated mortality.

Although the factors responsible for the anti-fibrotic action of CoQ10 have yet to be fully elucidated, its antioxidant and anti-inflammatory functions are thought to be major contributors to its clinical efficacy in the treatment of this age-related disorder.[100]

Breast cancer: With TAM reduces cancer markers

In breast cancer patients, it is not the primary tumor, but its metastases at distant sites that are the main cause of death. Circulating breast cancer tumour markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA 15-3) are reliable indicators of impending relapse, in which an increasing tumor marker level is associated with a very likelihood of developing recurrence. In the present study, 84 breast cancer patients were randomized to receive a daily supplement of 100 mg coenzyme Q10 (CoQ10), 10 mg riboflavin and 50 mg niacin (CoRN) one dosage per day along with 10 mg tamoxifen (TAM) twice a day. Serum CEA and CA 15-3 levels were elevated in untreated breast cancer patients (group II) and their tumour

marker levels significantly reduced upon tamoxifen therapy for more than 1 year (group III). Group III patients supplemented with CoRN for 45 d (group IV) and 90 d (group V) along with tamoxifen significantly reduced CEA and CA 15-3 levels. This study suggests supplementing CoRN to breast cancer patients along with tamoxifen reduces the serum tumor marker level and thereby reduce the risk of cancer recurrence and metastases. [76]

Breast cancer study II: Reduces angiogenic markers

Tumor angiogenesis is a complex mechanism consisting of multi-step events including secretion or activation of angiogenic factors by tumour cells, activation of proteolytic enzymes, proliferation, migration and differentiation of endothelial cells. Both primary and metastatic tumors in the breast are dependent on angiogenesis. In the present study, 84 breast cancer patients were randomized to receive a daily supplement of CoQ(10) 100 mg, riboflavin 10 mg and niacin 50 mg (CoRN), one dosage per day along with tamoxifen (TAM) 10 mg twice a day. Serum pro-angiogenic levels were elevated in untreated breast cancer patients (Group II) and their levels were found to be reduced in breast cancer patients undergoing TAM therapy for more than 1 year (Group III). When these group III breast cancer patients were supplemented with CoRN for 45 days (Group IV) and 90 days (Group V) along with TAM, a further significant reduction in pro-angiogenic marker levels were observed. Supplementing CoRN to breast cancer patients has found to decrease the levels of pro-angiogenic factors and increase the levels of anti-angiogenic factors. A reduction in pro-angiogenic marker levels attributes to reduction in tumor burden and may suggest good prognosis and efficacy of the treatment, and might even offer protection from cancer metastases and recurrence.[77]

Coenzyme Q_0 defeats NLRP3-mediated inflammation, EMT/metastasis, and Warburg effects by inhibiting HIF-1α expression in human triple-negative breast cancer cells

Coenzyme Q_0 (CoQ_0) is a derivative quinone from Antrodia camphorata (AC) that exerts anticancer activities. This study examined the anticancer attributes of CoQ_0 (0-4 μM) on inhibited anti-EMT/metastasis and NLRP3 inflammasome, and altered Warburg effects via HIF-1α inhibition in triple-negative breast cancer (MDA-MB-231 and 468) cells. MTT assay, cell migration/invasion assays, Western blotting, immunofluorescence, metabolic reprogramming, and LC-ESI-MS were carried out to assess the therapy potential of CoQ_0. CoQ_0 inhibited HIF-1α expression and suppressed the NLRP3 inflammasome and ASC/caspase-1 expression, followed by downregulation of IL-1β and IL-18 expression in MDA-MB-231 and 468 cells. CoQ_0 ameliorated cancer stem-like markers by decreasing CD44 and increasing CD24 expression. Notably, CoQ_0 modulated EMT by upregulating the epithelial marker E-cadherin and downregulating the mesenchymal marker N-cadherin. CoQ_0 inhibited glucose uptake and lactate accumulation. CoQ_0 also inhibited HIF-1α downstream genes involved in glycolysis, such as HK-2, LDH-A, PDK-1, and PKM-2 enzymes. CoQ_0 decreased extracellular acidification rate (ECAR), glycolysis, glycolytic capacity, and glycolytic reserve in MDA-MB-231 and 468 cells under normoxic and hypoxic ($CoCl_2$) conditions. CoQ_0 inhibited the glycolytic intermediates lactate, FBP, and 2/3-PG, and PEP levels. CoQ_0 increased oxygen consumption rate (OCR), basal respiration, ATP production, maximal respiration, and spare capacity under normoxic and hypoxic ($CoCl_2$) conditions. CoQ_0 increased TCA cycle metabolites, such as citrate, isocitrate, and

succinate. CoQ0 inhibited aerobic glycolysis and enhanced mitochondrial oxidative phosphorylation in TNBC cells. Under hypoxic conditions, CoQ_0 also mitigated HIF-1α, GLUT1, glycolytic-related (HK-2, LDH-A, and PFK-1), and metastasis-related (E-cadherin, N-cadherin, and MMP-9) protein or mRNA expression in MDA-MB-231 and/or 468 cells. Under LPS/ATP stimulation, CoQ_0 inhibited NLRP3 inflammasome/procaspase-1/IL-18 activation and NFκB/iNOS expression. CoQ_0 also hindered LPS/ATP-stimulated tumor migration and downregulated LPS/ATP-stimulated N-cadherin and MMP-2/-9 expression. The present study revealed that suppression of HIF-1α expression caused by CoQ_0 may contribute to inhibition of NLRP3-mediated inflammation, EMT/metastasis, and Warburg effects of triple-negative breast cancers.[116]

Modulates MMP-2 activity in MCF-7 cell line as a breast cancer cellular model.

Matrix Metalloproteinases 2 is a key molecule in cellular invasion and metastasis. Mitochondrial ROS has been established as a mediator of MMP activity. Coenzyme Q(10) contributes to intracellular ROS regulation. Coenzyme Q(10) beneficial effects on cancer are still in controversy but there are indications of Coenzyme Q(10) complementing effect on tamoxifen receiving breast cancer patients. In this study we aimed to investigate the correlation of the effects of co-incubation of coenzyme Q10 and N-acetyl-L-cysteine (NAC) on intracellular H2O2 content and Matrix Metalloproteinase 2 (MMP-2) activity in MCF-7 cell line. The results showed that both coenzyme Q10 and N-acetyl-L-cysteine reduce MMP-2 activity along with the pro-oxidant capacity of the MCF-7 cell in a dose proportionate manner.[86]

Protective mechanisms of coenzyme-Q10 may involve up-regulation of testicular P-

glycoprotein in doxorubicin-induced toxicity.

The anticancer drug; doxorubicin (DOX), causes testicular toxicity as an adverse effect. P-glycoprotein (P-gp) is a multidrug resistance efflux transporter expressed in blood-testis barrier, which extrudes DOX from the testis. We investigated whether DOX-induced gonadal injury could be prevented by the use of antioxidant; coenzyme-Q10 (CoQ10). The involvement of P-gp expression, as a possible protective mechanism, was also investigated. CoQ10 was administered orally for 8 days, and DOX toxicity was induced via a single i.p. dose of 15 mg/kg at day 4. Concomitant administration of CoQ10 with DOX significantly restored testicular oxidative stress parameters and the distorted histopathological picture, reduced the up-regulation of caspase 3 caused by DOX, and increased P-gp expression. We show for the first time that CoQ10 up-regulates P-gp as a novel mechanism for gonadal protection. In conclusion, CoQ10 protects against DOX-induced testicular toxicity in rats via ameliorating oxidative stress, reducing apoptosis and up-regulating testicular P-gp.[93]

Melanoma

Abnormally low concentrations of CoQ10 were found to be a strong predictor of metastasis in patients with melanoma. Patients with melanoma and matched controls were followed over seven and one-half years. The average CoQ10 levels of patients at baseline was 0.50 mcg/ml compared to 1.27 mcg/ml in controls. It was found than 33 percent of melanoma patients developed metastases during the follow-up period. The patients who developed metastases during follow-up had baseline CoQ10 levels of 0.34 mcg/ml compared with a level of 0.57 mcg/ml in patients who did not develop metastases. Patients with low baseline CoQ10 levels had an approximate eight-fold risk of metastatic disease compared with patients with high levels. It was

concluded the baseline CoQ10 levels are a powerful and independent prognostic factor that can be used to estimate the risk for melanoma progression. A The foregoing study suggests the probability that CoQ10 supplementation may greatly reduce the risk of metastases in melanoma patients.[84]

Improved survival in patients with end-stage cancer treated with coenzyme Q(10) and other antioxidants: a pilot study

This pilot study evaluated the survival of patients with end-stage cancer who received supplements of coenzyme Q(10) and a mixture of other antioxidants (e.g. vitamin C, selenium, folic acid and beta-carotene). During a period of 9 years, 41 patients who had end-stage cancer were included. Forty patients were followed until death and one patient was lost to follow-up and presumed dead. Primary cancers were located in the breast, brain, lungs, kidneys, pancreas, oesophagus, stomach, colon, prostate, ovaries and. The median predicted survival time was calculated from Kaplan- Meier curves for each patient at inclusion. Median predicted survival was 12 months (range 3 – 29 months), whereas median actual survival was 17 months (1 – 120 months), which is > 40% longer than the median predicted survival. Mean actual survival was 28.8 months versus 11.9 months for mean predicted survival. Ten patients (24%) survived for less time than predicted, whereas 31 (76%) survived for longer. Treatments were very well tolerated with few adverse effects.[85]

Skin health

The functional loss of mitochondria represents an inherent part in modern theories trying to explain the cutaneous aging process. The present study shows significant age-dependent differences in mitochondrial function of keratinocytes isolated from skin biopsies of

young and old donors. Our data let us postulate that energy metabolism shifts to a predominantly non-mitochondrial pathway and is therefore functionally anaerobic with advancing age. CoQ{10} positively influences the age-affected cellular metabolism and enables to combat signs of aging starting at the cellular level. As a consequence topical application of CoQ10 is beneficial for human skin as it rapidly improves mitochondrial function in skin in vivo. [70]

Coenzyme Q{10} (CoQ{10}) was reported to reduce ROS production and DNA damage triggered by UVA irradiation in human keratinocytes in vitro. Further, CoQ10 was shown to reduce UVA-induced MMPs in cultured human dermal fibroblasts. We speculated that UVB radiation-induced cytokine production in keratinocytes may be inhibited by CoQ{10}, resulting in the reduction of MMPs in fibroblasts leading to wrinkle reduction. Our in vitro studies showed that UVB-induced IL-6 production of normal human keratinocyte (NHKC) decreased in the presence of CoQ{10}. Furthermore, MMP-1 production of fibroblasts cultured with the medium containing CoQ{10} collected from UVB-irradiated NHKC significantly decreased during 24 h culture. In the clinical trial study, we found that the use of 1% CoQ_{10} cream for five months reduced wrinkle score grade observed by a dermatologist. Taken together, our results indicate that CoQ_{10} may inhibit the production of IL-6 which stimulate fibroblasts in dermis by paracrine manner to up-regulate MMPs production, and contribute to protecting dermal fiber components from degradation, leading to rejuvenation of wrinkled skin.[78]

The Role of Coenzyme Q10 in Skin Aging and Opportunities for Topical Intervention

Background: Coenzyme Q10 (CoQ10) is a naturally produced, lipid-soluble molecule crucial for cellular energy production and antioxidant activity. It diminishes with age and under external stress factors in skin,

leading to signs of aging. Beyond its role in cellular energy production within the mitochondria, CoQ10 is vital to skin's defense against oxidative stress, a key contributor to premature aging. Use of topical skincare products with CoQ10 can be effective to replenish levels of CoQ10 and reverse skin aging.

Objective: This publication discusses the role of CoQ10 in skin aging along with the benefits of topical skincare products that incorporate CoQ10 as an ingredient.

Methods: We searched the PubMed database using terms "Coenzyme Q10" and "skin" and "aging." Overall, the search yielded 80 results, but a limitation of 10 years was then applied to restrict publications to those with the most up-to-date science.

Results: A total of 36 publications were identified and included as background for this article. These 36 publications encompassed both original research articles and review articles.

Discussion: Applying topical skincare products with CoQ10 replenishes CoQ10 cellular levels, helping to normalize cellular energy homeostasis and providing antioxidative effects to support and repair cutaneous damage including signs of skin aging. In *ex vivo* and *in vivo* studies, application of CoQ10 increased CoQ10 levels both on the skin surface (i.e., stratum corneum) and even more in deeper levels of the skin. Clinically, topical application of CoQ10-formulated products reduces the depth of cutaneous wrinkles, a sign associated with aging.

Conclusion: Aging and stressed skin are, in part, the result of alterations in cellular metabolic homeostasis, which can be reversed via the benefits of topical application of CoQ10-enriched formulations that stimulate cutaneous energy metabolism and reduce free radicals via antioxidant function. By restoring physiological homeostasis, topical skincare products with CoQ10 replenish the skin's antioxidant levels,

increase cellular (energy) metabolism, and reduce the signs of skin aging.[119]

Periodontal Disease

I can remember back in the mid 1980's when CoQ 10 first hit the shelves of health food stores around America it was being touted solely for periodontal gum disease. I can also clearly remember after recommending it to a number of people with this condition and seeing how it repeatedly improved and even reversed the gum disease in these people that this is a really special compound. Deficiency of CoQ10 in the gums of people affected by periodontal disease has been shown in numerous investigations.[38, 39] Seven patients with periodontal disease were given 25 mg CoQ10 twice daily in capsules and showed remarkable healing within days in this open study.[40] A double-blind trial using the same protocol showed a significant benefit in healing gingival tissue over three weeks time without adverse effects in 18 patients.[41]

Pre-eclampsia

CoQ10 may reduce the risk of developing pre-eclampsia in women at risk for this condition. According to the results of a randomized, double-blind, placebo-controlled trial, women receiving 200 mg of CoQ10 a day had a 10% lower risk of developing pre-eclampsia than women on placebo. One hundred and ninety-seven women completed the study, and the overall rate of pre-eclampsia was 20%. For women receiving the placebo, 30 of them developed pre-eclampsia, equivalent to 25.6 of women in this group. On the other hand, only 17 women, or 14.4 per cent, in the CoQ10 group developed pre-eclampsia. The difference between the groups was statistically significant, added the researchers. *"The results of this study support the hypothesis that CoQ10 supplementation given prophylactically from 20 weeks of*

pregnancy leads to a reduction in the rate of pre-eclampsia in women at risk for the condition," wrote the researchers.[82]

Athletics

Athletes may find that CoQ10 supplementation improves physical performance. A study in 25 world-class cross-country skiers found that 90 mg CoQ10 daily improved their performance and reduced recovery times compared to placebo.[42] Basketball players and runners also had improvements while taking 100 mg daily in separate controlled studies.[43, 44] Not all studies have been able to confirm these findings.[45, 46] One study involving male cyclists and triathletes, using 1 mg/kg body weight CoQ10, could find no improvements in oxygen uptake or other measures of improved performance after one month.[47]

Migraine headaches

CoQ10 may aid migraine headaches by stimulating the mitochondria to produce more energy. A 2002 study published in the journal Cephalgia reported on 32 migraine patients treated with a daily dose of 150 mg of CoQ10 for four months. By the study's end, the average number of migraine attacks per month fell from 4.85 to 2.81, and CoQ10 did not trigger any reported side effects. If the results of this preliminary study are confirmed by double-blind studies, 150 mg per day of CoQ10 may become the recommended dose. [60]

Enhances Anti-inflammatory effects of Vitamin E: Lowers CRP

Inflammation and oxidative stress are key factors in the development and progression of vascular diseases, including heart disease, the world's biggest killer.

The combination supplement over a two-week period on 21 baboons that had previously been fed a high-fat, high-cholesterol diet for seven weeks. The vitamin E (DL-alpha tocopheryl acetate) reduced blood levels of C-reactive protein, a well-established marker for inflammation, from 0.91 to 0.43 mg/dL, a 53 per cent reduction. Additional supplementation of 2g CoQ10 per kg diet, donated by the leading supplier Kaneka, further reduced serum CRP by nearly 70 per cent. [65]

Improves health of people living with HIV

High-dose coenzyme Q therapy may increase the general well being of asymptomatic HIV-infected patients and those with lipodystrophy, but may aggravate pain in those with peripheral neuropathy. The study also supports an association between low mitochondrial DNA (mtDNA) levels in HIV-infected patients receiving highly active antiretroviral therapy (HAART) and peripheral neuropathy and lipodystrophy. Investigators used real-time PCR to measure mtDNA levels in subcutaneous abdominal fat and peripheral blood mononuclear cells (PBMCs) in 25 HIV-infected patients on HAART and 10 HIV-seronegative healthy control subjects. Among the HIV-infected group, 13 had lipodystrophy, 5 had peripheral neuropathy, and 7 had neither. The mean number of mtDNA copies per cell was lower in fat tissue from

HIV-infected patients with peripheral neuropathy (1547 mtDNA copies/cell), lipodystrophy (1732 mtDNA copies/cell) and in the seven patients with no adverse effects (2935 mtDNA copies/cell) compared with healthy controls (6198mtDNA copies/cell). There was “no clear difference” between the groups in the mtDNA content of PBMCs, Dr. Eva Rabing Christensen and colleagues from Aarhus University Hospital report in the November 1st issue of Clinical Infectious Diseases. Therefore, for predictive purposes, measurement of mtDNA

levels in fat biopsy specimens “seems superior” to measurement of mtDNA levels in PBMCs, they note.

Treatment with coenzyme Q (100 mg twice daily for 3 months) as opposed to placebo “improved the general condition of patients, generally resulted in increased weight in patients with lipodystrophy, but initially and reversibly aggravated peripheral neuropathy symptoms,” the team also reports. Coenzyme Q therapy, ” increased the oxidative capacity at the cellular level,” did not appear to alter mtDNA levels in fat tissue or PBMCs relative to placebo, according to the investigators. This study, they conclude, shows that coenzyme Q therapy does have an effect on patients with lipodystrophy and peripheral neuropathy. “The exact benefit and the mechanisms behind this benefit, however, will need to be resolved in subsequent studies,” they emphasize. [66]

The T4/T8 ratios of lymphocytes are known to be low in patients with AIDS, ARC and malignancies. Our two patients with ARC have survived four-five years without any symptoms of adenopathy or infection on continuous treatment with CoQ10. We have newly found that 14 ordinary subjects responded to CoQ10 by increases in the T4/T8 ratios and an increase in blood levels of CoQ10; both by p less than 0.001. This knowledge and survival of two ARC patients for four-five years on CoQ10 without symptoms, and new data on increasing ratios of T4/T8 lymphocytes in the human by treatment with CoQ10 constitute a rationale for new double blind clinical trials on treating patients with AIDS, ARC and diverse malignancies with CoQ10.[67]

Coenzyme Q10 improves fibromyalgia

Individuals with fibromyalgia have also been shown to present with mitochondrial dysfunction and significantly reduced coenzyme Q10 concentrations.[102, 102]

Further evidence suggests that levels of oxidative stress and mitochondrial dysfunction, through coenzyme Q10 levels are correlated with fibromyalgia symptoms.[104]

Supplementation of coenzyme Q10 has been shown within this review to improve these markers and the symptoms of fibromyalgia.[105, 106, 107,108]

Drug Interactions

Warfarin: There is **ONE** report of CoQ10 decreasing the effectiveness of warfarin. [68]

Statins: CoQ10 and cholesterol share the same metabolic pathways. Inhibition of the enzyme 3-hydroxyl-3-methylglutonyl coenzyme A (HMG-CoA) reductase would be expected to decrease CoQ10 levels. The statin drugs lovastatin, simvastatin and pravastatin are known to decrease CoQ10 levels in humans. It is likely that all statins have this effect.

Doxorubicin: CoQ10 may help ameliorate the cardiotoxicity of doxorubicin.

Antidiabetic medications: CoQ10 may improve glycemic control in some type II diabetics. If this were to occur, antidiabetic medications might need appropriate adjusting.

Beta Blockers: Some beta blockers, in particular propanolol, have been reported to inhibit some CoQ10-dependent enzymes

Piperine: Piperine, found in black pepper, may increase plasma levels of CoQ10.

Dosage:

I dosage I use in clinic are inline with what the research confirms. 30 mg. Up to 600 mg. daily taken in a fatty emulsified form, or with fat.

Also Bioprine, a pepper extract may enhance bioavailability. Given the lack of toxicity of CoQ10, even at doses as high as 1000 mg daily for years, [57] along with its apparent immense beneficial effects supplementation should be considered most age-related disease, or just as prophetic agent to reduce the aging process.

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