

# Coenzyme Q10 deficiency in elderly: Can nutritional supplementation play a role? Mini review

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## ABSTRACT

Coenzyme Q10 (CoQ10), an important mitochondrial redox component, plays a pivotal role in cellular energy production; moreover, it is the only lipid-soluble antioxidant endogenously synthesized in humans. Given its function and physiological importance, it is not surprising that CoQ10 deficiency may result in several diseases. With aging, humans begin to lose the ability to synthesize CoQ10 from food, resulting in reduced serum levels of CoQ10 and contributing to aging-associated symptoms. Poor eating habits, infections, stress and also some drugs, as beta blockers, antihypertensive agents and statins, may reduce serum levels of CoQ10. Dietary supplementation has been proposed as key strategy to increase CoQ10 availability, improving health status in elderly; however CoQ10 is not approved by U.S. Food and Drug Administration for the treatment of any medical condition and it is sold only as a dietary supplement. Aim of the study was to examine the latest relevant evidences on potential benefits of CoQ10 nutritional supplement and its implication in improving health status in elderly. There is evidence that, in elderly, oral administration of CoQ10 reduces oxidative stress and inflammatory markers and reduces cardiovascular mortality; in diabetics CoQ10 treatment improves insulin sensitivity and decreases glycated hemoglobin. Therapeutic benefit from CoQ10 supplementation has also been obtained in neurodegenerative diseases as Parkinson's, Alzheimer's and Huntington's diseases. CoQ10 supplements could be useful in several aging-related clinical conditions; however, well standardized long-term and larger further studies are needed

**Keywords:** coenzyme Q10, elderly, supplementation

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Coenzyme Q10 (CoQ10) is an important mitochondrial redox component that plays a pivotal role in cellular energy production as essential cofactor in oxidative phosphorylation. CoQ10 is present in all the biological membranes, mostly in the phospholipid membrane of the mitochondria, where it also acts as cell membrane stabilizing and potent intracellular scavenger of free radicals [1].

Organs with utmost energy needs as brain, heart, kidney and liver have the highest concentrations of

CoQ10 and its omnipresence throughout the body gave alternate name, Ubiquinone [1, 2]. Moreover, this enzyme is the only lipid-soluble antioxidant endogenously synthesized in humans [2]; however, the endogenous production of CoQ10 begin to progressively decrease after the age of 20 [3], so that with aging humans lose the ability to synthesize CoQ10 from food, resulting in reduced serum levels of this important antioxidant factor [4]. Poor eating habits, infections, stress and also some drugs, as beta



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blockers, antihypertensive agents and statins, may reduce serum levels of CoQ10 [5-7]. In humans, the daily requirement for CoQ10 is 3-6 mg, derived primarily from meat, particularly organ meats as kidney, liver, heart and beef; fish as sardines and mackerel; soy oil and peanuts are also rich source of dietary CoQ10 [8].

CoQ10 is gaining popularity in cosmetic and anti-ageing industries [9-12] but, given its function and physiological importance, it is not surprising that CoQ10 deficiency contributes to aging-associated symptoms and may result in several diseases [4]. For this reason, dietary supplementation has been proposed as a key strategy to increase CoQ10 availability, improving health status in elderly [6]; however CoQ10 is not approved by U.S. Food and Drug Administration for the treatment of any medical condition and it is sold only as a dietary supplement. Yet, although CoQ10 deficiency is more relevant in elderly, there was poor interest in researchers regarding to potential benefits that CoQ10 dietary supplements could have in older people. Aim of this research was to examine the latest relevant evidences on potential benefits of CoQ10 nutritional supplement and its implication in improving health status in elderly.

## METHODS

A review of recent literature has been carried out via Pub Med database, using these search term: coenzyme Q10, elderly, supplementation. Search was not limited by language or human subjects. All the found items, published in the last five years, from January 2013 to December 2017, were analysed. Article types was determined using filters available on PubMed database. Additional articles were selected from the bibliographies of the quoted references. Other data were deduced from retrospective analysis and by careful assessment of the obtained items and their references.

## RESULTS

Eighty items were obtained: 59 were clinical studies/trials, including 55 randomized controlled

trials, 4 multicenter studies, 5 comparative studies; 3 reviews and 4 case reports were also found. Five studies were conducted in animal models. Observational studies were not found, neither meta-analysis nor guidelines nor consensus. Remaining items were prevalently other journal articles or other publication types.

In summary, the analysis of obtained data primarily showed that, in elderly, oral administration of CoQ10 reduces oxidative stress, inflammatory markers and cardiovascular mortality; positive effects of CoQ10 supplementation on oxidative stress were also observed in subjects with chronic kidney disease. Moreover in diabetic patients CoQ10 treatment improves insulin sensitivity and decreases glycated hemoglobin. Therapeutic benefit from CoQ10 supplementation has also been obtained in neurodegenerative diseases as Parkinson's, Alzheimer's and Huntington's. Lastly, there is some evidence that, in patients with breast and other types of cancer, CoQ10 supplementation seems associated with improvement of cancer-related fatigue. Generally, no toxicity was observed with varying doses of CoQ10 used in the different studies.

## DISCUSSION

There is promising evidence that oral administration of CoQ10 improves health status in elderly and slows the deterioration in health-related quality of life [13, 14]. Increasing evidence were found particularly in patient with cardiac diseases; the heart muscle uses more energy than any other tissue and normally it has the highest concentration of CoQ10, so it is very sensitive to CoQ10 deficiency [15].

In the past, it has been observed that nutritional supplements of CoQ10 make improvements of heart muscle function in patients with chronic heart failure [16]. In healthy elderly subjects higher serum levels of ubiquinol were found associated with lower serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a marker for chronic heart failure [17]. Moreover, in a cohort of community-dwelling elderly, long-term supplementation of CoQ10 and selenium has reduced NT-proBNP levels and cardiovascular mortality [18]; the same results were also achieved in

a 5-year prospective randomized double-blind placebo- controlled trial, carried out among elderly Swedish citizens [19]. Reduced cardiovascular mortality, in subjects receiving nutritional supplements of CoQ10, was confirmed in other studies among healthy elderly [20], also after a 10-year follow-up period [21], and in patients with chronic heart failure [15].

There is evidence that in patients with coronary artery disease, CoQ10 supplementation is able to reduce oxidative stress and inflammatory markers as Interleukin-6, increasing antioxidant enzyme activity [22, 23]; this benefit was also found in type 2 diabetic patients with stable coronary heart disease [24] and in veterans with stenosis of one major coronary artery during statins therapy [25].

Benefits for cardiovascular patients could also be related to other effects of CoQ10: it has been shown that long-term CoQ10 supplementation improves endothelium-dependent vasodilation in senescent rats, enhancing arterial relaxation and lowering blood pressure [26]; in humans, oral doses of CoQ10, varying from 75 to 600 mg daily, allowed to reduce the need to multidrug antihypertensive regimens [27]. Even in hypertensive patients daily supplementation of CoQ10 can be effective in decreasing some pro-inflammatory factors, such as Interleukin-6 and high-sensitivity-C reactive protein [28]. In some studies dietary supplementation with CoQ10 was also associated with improvement in lipid pattern of hypercholesterolemic patients [29-31], although in these studies CoQ10 was not administered alone, but in combination with other nutraceuticals. Some studies have also shown that CoQ10 supplementation effectively reduced statin-related muscular symptoms [32, 33]; nevertheless, other studies revealed no significant effects of CoQ10 on statin-induced myopathy and rhabdomyolysis, compared with placebo [34, 35].

With age, there is a decline in renal function and the incidence of kidney failure increases in elderly; in addition, given the high burden of risk factors for kidney disease in the middle-aged population, the high prevalence of chronic kidney disease in the elderly is not surprising [36, 37]. Compared with younger adults, older adults with advanced kidney disease have multiple comorbidities and a higher risk of death [38]; moreover, in patients with chronic renal failure and in

those receiving maintenance hemodialysis for end-stage renal disease there is an increased risk of cardiovascular disease, attributable to excess of oxidative stress [39, 40]. The effect of CoQ10 supplementation on oxidative stress was also assessed in subjects with chronic kidney disease and in hemodialysis patients, but conflicting as well as non unique results were found in our search [41-43].

The effects of CoQ10 were also investigated in diabetic patients: positive effects of a nutraceutical combination, including CoQ10, on lipid profile and glucose plasma levels were reported in a systematic review of randomized controlled trials [44]. Few studies have investigated the effects of coenzyme Q10 supplementation in elderly diabetics, predominantly in type2 diabetic patients: it has been shown that CoQ10 supplementation can decrease glycosylated hemoglobin in overweight and obese patients with type 2 diabetes [45], but the effect on glycemic control was discordant [46, 47]; however, there is evidence that oral administration of CoQ10 counteracts oxidative stress in type 2 diabetics [46] and reduces circulating levels of reactive oxygen species in patients with nonproliferative diabetic retinopathy [48]. Lastly, in patients with metabolic syndrome oral coenzyme Q10 administration can have beneficial effects on serum insulin levels, homeostasis model of assessment-insulin resistance, homeostatic model assessment-beta cell function and plasma total antioxidant capacity concentrations when compared with placebo group [49]. Coenzyme Q10 has been considered for improving glycemic control through various mechanisms, including a decrease in oxidation stress and improvement in beta cell function, insulin sensitivity and endothelial function [44].

For at least 20 years, potential benefits from CoQ10 supplementation in the treatment of neurodegenerative diseases were investigated in animal models [50-53] and in humans [50, 54-56]. Parkinson's disease is a typical age-related neurodegenerative disease characterized by degeneration and progressive loss of dopaminergic neurons in the substantia nigra leading to several clinical manifestations including tremors, bradykinesia, akinesia, abnormal postural reflexes, rigidity and, in the advanced stage of the disease, cognitive impairment and dementia [57]. It has been suggested that oxidative stress can play a role in the etiology and

progression of Parkinson's disease and pathological studies in animal models suggest that mitochondrial dysfunction can be a key pathological mechanism in Parkinson's disease [58]. It has been demonstrated that, in mice, CoQ10 can protect against striatal lesions produced by the mitochondrial toxins malonate and 3-nitropropionic acid and it also protects against 1-methyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity [50, 59, 60]. Some studies [55, 56, 61, 62] have shown beneficial effects of oral CoQ10 supplementation in Parkinson's patients, while in other studies [63, 64] CoQ10 showed no evidence of clinical benefit. However, a recent review [65] has established that the supplementation with CoQ10 does not slow functional decline nor provide any symptomatic benefit for patients with Parkinson's disease; moreover, data from a subsequent meta-analysis of randomized controlled trials [66] performed to assess the efficacy of CoQ10 supplementation in the treatment of Parkinson's disease, have confirmed that CoQ10 is not superior to placebo in terms of motor symptoms, although it has been shown safe and well tolerated. Then, at present, CoQ10 supplements appear to have a limited role in the prevention or treatment, as primary or adjunctive therapy, of Parkinson's.

Increasing evidence suggests that Alzheimer's disease is associated with oxidative damage that is caused in part by mitochondrial dysfunction which has been identified as an early event in Alzheimer's pathogenesis [67]. In vitro and in vivo analysis have suggested the neuroprotective potentials of CoQ10 in Alzheimer disease [68, 69]. It is assumed that the antioxidant capacity of this compound can slow down neurodegeneration and improve cognitive functions and functional decline by facilitating ATP synthesis and counteracting mitochondrial dysfunction. Clinical studies for the evaluation of neuroprotective effect, safety and tolerability of CoQ10 in mild to moderate Alzheimer patients will be required.

Huntington's disease is a rare genetic neurodegenerative disorder, characterized by progressive death of striatal and cortex neurons. Typically, the onset of symptoms is in middle-age, but this disorder can manifest at any time between infancy and senescence. Main clinical manifestation of Huntington's disease are hyperkinetic movements, behavioural difficulties, weight loss and progressive cognitive decline leading to death 15 to 20 years after

the onset of symptoms [70]. Various lines of evidence have produced the involvement of mitochondrial dysfunction in the pathogenesis of Huntington's disease [71] and some studies have dashed hopes that CoQ10 could have disease-modifying properties and play a therapeutic role in Huntington's disease [51, 52, 54]. In this regard, in our search we have found poor and weak clinical evidences [72, 73], then further studies will be needed.

Oxidative stress and resulting cellular DNA damage have been suggested to play a role in the etiology of several chronic diseases, including cancer [74-76] and decreased levels of CoQ10 were found in plasma of women with breast cancer [77] and cervical cancer [78] as well as in melanoma patients [79]. We have found some evidence in which CoQ10 supplementation seems associated with beneficial effect on DNA damage via p53-dependent DNA repair machinery in elderly subjects [80-82]. Moreover, in the past, few small studies have reported the ability of CoQ10 supplementation in ameliorating cardiotoxicity, liver toxicity and tolerability of cancer treatments, particularly in patients receiving chemotherapy with anthracyclines [83, 84]. Lastly, CoQ10 was often used in patients with breast and other cancers to improve tumor-related fatigue [85]. Unfortunately, at present, clinical investigations in older cancer patients are too limited; in our research we have found only a randomized, double-blind, placebo controlled study of CoQ10 in women (median age 52 years) with breast cancer and planned adjuvant chemotherapy, in which CoQ10 supplementation did not result in improved self-reported fatigue or quality of life [86]. In summary, although there are several evidences supporting potential benefits of CoQ10 supplementation in cancer patients, clinical results seem too weak and not very effective; hence, even in this field further studies will be needed.

With regard to safety and tolerability of CoQ10 dietary supplements, from our data it has emerged that CoQ10, generally, was well tolerated and no toxicity was observed; nevertheless, some adverse effects, mainly gastrointestinal, were observed with very high intake. Other potential side effects are rashes and headaches; yet, another aspect to consider is that the structure of CoQ10 is similar to vitamin K, therefore CoQ10 should be used with caution and accurate coagulation monitoring in patients taking oral



anticoagulant therapy, to avoid potential drug interactions [87-89].

Finally, CoQ10 is fat-soluble, so it is better absorbed when taken with a meal that contains oil or fat. Unfortunately, because of its hydrophobicity and large molecular weight, the absorption of dietary CoQ10 from the gastrointestinal tract is limited and its in vivo bioavailability is known to be poor. It was found that bioavailability of CoQ10 was significantly different depending on the formulations and dissolution could be one of the important factors affecting CoQ10 absorption; then, bile and the solubilized formulation are essential for absorption of CoQ10 [90]. Several novel formulations of CoQ10 have been developed to improve absorption and bioavailability of CoQ10 in an attempt to enhance its water solubility [91, 92]; solubilize formulations of CoQ10 proved to be clearly superior to oily dispersions and crystalline CoQ10 in their overall bioavailability [93], but also CoQ10 lipid-based formulations with a novel colloid delivery system, known as "colloidal-Q10", have been shown to improve the enteral absorption and the bioavailability of CoQ10 [94].

In summary, our data analysis leads to some considerations: 1) most clinical trials evaluating potential benefits of CoQ10 supplementation in elderly are small and short-term studies; the most significant data were obtained from various arms and sub-analysis of a 4-year double-blind randomized placebo-controlled intervention trial, carried out among 443 Swedish citizens with long-term follow-up from 5 to 10 years [19-21]; 2) in several studies enrolled patients were not evermore homogeneous by age and health status; 3) in many studies CoQ10 was co-administered with other nutraceuticals or dietary supplements, particularly selenium but also n-3 fatty acids, monacolin K, policosanol, vitamins, folic acid, resveratrol and others; 4) although most commonly used CoQ10 dosage was 100-200 mg daily, in the different studies CoQ10 supplements were administered in considerably variable dosing regimens, from 20 mg up to 1800 mg daily and more; lower doses were used in studies involving co-administration of CoQ10 with other dietary supplements; 5) Ubiquinol, a reduced form of CoQ10 with increased polarity and better intestinal absorption

and bioavailability, was the most used in clinical trials but not evermore.

## CONCLUSION

Our data confirm the evidence that oral supplementation of CoQ10 can improve several aging-related clinical conditions and slow the deterioration in health-related quality of life; CoQ10 benefits seem linked primarily to its antioxidant properties. Therefore CoQ10 nutritional supplement could be useful in improving health status in elderly, but main limit to its efficacy seems linked to its oral absorption and relative low bioavailability. Dietary supplements of CoQ10 seem well tolerated and no toxicity was observed though some adverse effects, largely gastrointestinal, were observed with very high intake. Unfortunately, the clinical evidences are often poor and weak as well as conflicting, so that well standardized long-term and larger further studies will be needed, also to establish the most effective dosage and the most bioavailable formulation.

### *Authorship declaration*

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

### *Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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