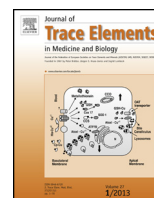




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Clinical studies

Selenium and coenzyme Q10 interrelationship in cardiovascular diseases – A clinician's point of view

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ABSTRACT

A short review is given of the potential role of selenium deficiency and selenium intervention trials in atherosclerotic heart disease. Selenium is an essential constituent of several proteins, including the glutathione peroxidases and selenoprotein P. The selenium intake in Europe is generally in the lower margin of recommendations from authorities. Segments of populations in Europe may thus have a deficient intake that may be presented by a deficient anti-oxidative capacity in various illnesses, in particular atherosclerotic disease, and this may influence the prognosis of the disease.

Ischemic heart disease and heart failure are two conditions where increased oxidative stress has been convincingly demonstrated. Some of the intervention studies of anti-oxidative substances that have focused on selenium are discussed in this review. The interrelationship between selenium and coenzyme Q10, another anti-oxidant, is presented, pointing to a theoretical advantage in using both substances in an intervention if there are deficiencies within the population. Clinical results from an intervention study using both selenium and coenzyme Q10 in an elderly population are discussed, where reduction in cardiovascular mortality, a better cardiac function according to echocardiography, and finally a lower concentration of the biomarker NT-proBNP as a sign of lower myocardial wall tension could be seen in those on active treatment, compared to placebo.

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Introduction

In the western hemisphere, the impact of cardiovascular diseases are important both for the individual as well as for the society. It has been convincingly shown that in most of the different cardiac diseases, atherosclerosis plays a major role. It is therefore important to discuss the connection between cardiac disease, oxidative stress, and the clinical consequences of a possible treatment.

Oxidative stress in the body could be defined as an imbalance between anti-oxidative defence systems and free radicals. This could be seen both as a result of normal aging, but also as a consequence of disease [1,2]. The mitochondrion is the most important producer of endogenous reactive oxygen species (ROS), even though peroxisomes, lysosomes and the plasma membrane are also sources of ROS [3]. The mitochondrial DNA is the part of the cell

most susceptible to damage caused by oxidative stress, although proteins can also be functionally damaged by this stress. Zhou et al. presented data showing the connection between aging, increased aortic stiffness, and increased smooth muscle cell apoptosis as a result of oxidative stress [4]. Factors such as low antioxidant intake, and pollution can also increase ROS [5].

In cardiac disease, as seen in heart failure, the cytosolic and mitochondrial ROS become distorted, leading to oxidative imbalance, mitochondrial dysfunction and eventually to cell death [6]. It has been demonstrated that the more the cardiac function in this patient group is impaired, the more signs of apoptosis and oxidative stress appear [7–9]. In a study that included 281 patients with coronary heart disease, Heitzer et al. demonstrated increased vascular oxidative stress and endothelial dysfunction as a predictor of risk of cardiovascular events [10]. Vassalle et al. presented the same results in a small study [11]. The same patient group has also been shown to have increased inflammatory response caused by the oxidative stress. Abramson et al. presented data indicating a significant relation between the level of oxidative stress and level of inflammation, as measured by the biomarker high sensitivity C-reactive protein (hsCRP) [12].

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Selenium and cardiovascular diseases: From prevention to cardiac failure

Selenium is an essential nutrient and one of the most important antioxidants in the body, and it is also involved in immune surveillance [13–15]. It is found within the body mainly as selenomethionine or as selenocystein in various selenoproteins. Of those, glutathione peroxidase (GPx), thioredoxin reductase and selenoprotein P are some of the most important [16].

In the French SU.VI.MAX (SUpplementation en Vitamines et Minéraux AntioXydants) study where an intervention using several antioxidants including selenium was performed, no effect on cardiovascular mortality could be seen [17]. However, the population was not at risk of selenium deficiency as the average selenium concentration in plasma at baseline was 1.09 $\mu\text{mol/L}$ in women and 1.14 $\mu\text{mol/L}$ in men.

Animal studies have shown that GPx1 protects against virus-induced myocarditis [18], and also protects against atherosclerosis in diabetic apolipoprotein E deficient mice [19], and thus has a beneficial effect on cardiovascular disease in these models.

Patients that are critically ill have signs of increased oxidative stress. Research on this patient group has been extensive, including in regard to anti-oxidative intervention. One of the most powerful anti-oxidative trace elements is selenium. Much interest has therefore been focused on selenium in conditions of increased or expected oxidative stress.

In one study that included patients with systemic inflammatory response syndrome (SIRS) and multi-organ dysfunction syndrome (MODS), it could be demonstrated that the patients had a 40% decreased level of s-selenium, and also a deficiency in one of the main selenium-containing enzymes, glutathione peroxidase (GPx), compared to healthy individuals. Also, those with low levels of selenium or GPx had a significantly higher risk of developing SIRS and MODS. The authors discuss a possible mechanism based on the fact that a deficiency of selenium could activate the nuclear transcription factor kappa B (NF κ -B) and promote vasoconstriction and coagulation, as seen in SIRS [20].

Stoppe et al. presented a study in 2011 in which 60 patients underwent cardiac surgery [21]. The use of extra-corporeal circulation has been shown to start systemic inflammation and also to induce ischemia reperfusion-related release of ROS [22–24]. The authors demonstrated that, preoperatively, 83% of the patients had a selenium deficiency, and that all patients had a decreased s-selenium level when reaching the intensive care unit after their operation. Evaluation of the trace element levels showed that the selenium levels could provide prognostic information regarding the development of MODS. Also, the postoperative serum selenium levels inversely correlated with the length of stay in the intensive care unit.

From the same research group, interesting results were published in 2013 when 100 patients who had been accepted for elective cardiac surgery, including extra-corporeal circulation, were evaluated [25]. Half of the study group was given sodium-selenite intravenously preoperatively and during the stay in the intensive care unit. Also, in this study population, 75% had preoperative selenium blood levels below the reference levels recommended in Germany. The authors demonstrated that a lower risk of multi-organ failure, and less respiratory organ dysfunction were found in those receiving selenium interventions.

Angstwurm et al. presented a double-blind, randomized placebo controlled multi-centre study from 11 different intensive care units in Germany. The study included 189 patients with sepsis, septic shock or severe systemic inflammatory syndrome [26]. Ninety-two patients received sodium-selenite at 1000 $\mu\text{g/day}$ for two weeks, and 97 patients received a placebo. In the per-protocol analysis, an absolute reduction of mortality of 14.3% could be seen. Therefore,

one in seven patients could be saved by using selenium treatment. The number of patients it was necessary to treat in order to save one was seven. In the group who had an APACHE III score of >102 indicating a high level of multi-organ involvement, a significantly lower mortality could be seen (OR: 0.28; 95%CI 0.08–0.97; $p=0.04$). The APACHE (Acute Physiology and Chronic Health Evaluation) score evaluates the severity of disease in patients treated in Intensive Care units, where the patient's age and 12 physiological measurements are included. The higher the score, the more serious the patient's disease.

In those with more than three organ failures, a significantly higher survival rate could be seen in the intervention group, compared to the placebo group (OR: 0.40; 95%CI 0.16–0.96; $p=0.039$). In the subgroup that suffered from intravascular coagulation, the survival rate in the intervention group was 59.5%, compared to 33.3% in the placebo group (OR: 0.34; 95%CI 0.14–0.84, $p=0.018$).

The possible association between ischemic heart disease and intake of selenium has been discussed in the literature for decades, and in one report a 2.9 fold increase in cardiovascular mortality could be found in those with a low selenium intake [27,28]. However, there are conflicting reports regarding the effectiveness of intervention with selenium on cardiovascular disease [29–32].

It should be pointed out that in some of the reports a short intervention time might explain the lack of effects. However, there are also other explanations, such as a deficiency of coenzyme Q10 (see below), but also a deficiency of one of the factors needed for efficient synthesis of the selenoproteins; isopentenyl Sec-tRNA [34]. Le Bouil et al. reported that patients with heart failure had a lower selenium concentration than those without heart failure [33], whereas Folkers et al. demonstrated that patients with heart failure had lower levels of coenzyme Q10 in myocardial cells compared to patients without heart failure [35].

Intake of selenium

The dietary intake of selenium differs throughout the world. In Europe the estimated mean intake of selenium is 40 $\mu\text{g/day}$ [36], whereas the mean intake in the US is estimated to be 134 $\mu\text{g/day}$ in men and 93 $\mu\text{g/day}$ in women [37]. The differences can mainly be explained by the poor selenium content of the soil in Europe, compared to the US, or the Australian soils [16]. In the French EVA (Etude du Vieillissement Artériel) study where an elderly population was evaluated, an association was demonstrated between low plasma concentration of selenium and mortality [38]. The recommended intake in order to obtain optimal plasma activity of the main enzymes glutathione peroxidase and selenoprotein P differs. Xia et al. presented data indicating that for a normal weighted (about 76 kg) Caucasian a selenium intake of 75 $\mu\text{g/day}$ would be necessary in order to optimize the function of selenoprotein P [39]. Hurst et al. demonstrated that a total selenium intake of 105 $\mu\text{g/day}$ was necessary to achieve optimal function of selenoprotein P, and also reported that a selenium deficiency might exist in most European countries [40]. In the Swedish KiSel (Swedish eponym for selenium and Q10 study in Kinda county/municipality) study, a selenium intake of 35 $\mu\text{g/day}$ was estimated, and the group with a selenium intake of 20–30 $\mu\text{g/day}$ profited even more by supplementation. Also, it has been proposed that a selenium intake of 75–125 $\mu\text{g/day}$ is necessary in order to obtain cancer protection [41].

Coenzyme Q10

Coenzyme Q10, or ubiquinone, which is present in all cells, has a central position in the mitochondrial respiratory chain as an electron carrier in the process of oxidative phosphorylation. It is

also a powerful anti-oxidant, mainly protecting against lipid peroxidation. The endogenous production of coenzyme Q10 declines after the age of 20, and at the age of 80, only half of the coenzyme Q10 production can be found in the heart [42]. Substantial efforts have been made in numerous studies where supplementation of coenzyme Q10 has been evaluated in different conditions, such as multiple sclerosis [43,44], in Parkinson's disease [45], in patients with renal injury treated with shockwave lithotripsy [46], in male infertility [47], and in heart disease, but results have been inconsistent [48–50]. In a meta-analysis consisting of 13 studies and 395 patients, Fotino et al. reported increased cardiac function after coenzyme Q10 supplementation [51]. Endothelial function has attracted attention due to being involved in the development of cardiac diseases, and positive effects of supplementation of coenzyme Q10 on endothelial function have been reported in the literature [52]. In a meta-analysis consisting of five studies including 194 patients Gao et al. reported significant improvement of the endothelial function as effect of intervention of coenzyme Q10, mainly measured as artery dilatation of the brachial artery [53].

In patients with cardiomyopathy, low concentrations of coenzyme Q10 have been found [54]. Also, in those with ischemic heart disease a low level of coenzyme Q10 has been reported, a level that further decreases as the disease progresses. Molyneux et al. also demonstrated in a multivariate analysis that the plasma concentration of coenzyme Q10 provided significant prognostic information regarding risk of cardiovascular death in a population of patients with chronic heart failure, thus indicating a possible rationale for intervention in this patient group [55].

The selenium and coenzyme Q10 interrelationship

Selenium in the form of the selenoprotein TrxR1, which contains a unique amino acid, the selenocysteine (SeC), in its active site, is needed for the cell to reduce coenzyme Q10 (ubiquinone) to the active form ubiquinol [56,57]. Also, the synthesis of the SeC-containing proteins requires a functional mevalonate pathway, where coenzyme Q10 is a product [34]. Xia et al. also demonstrated interesting data indicating a possible explanation for the conflicting data from some single intervention studies (Fig. 1) [56]. A deficiency of selenium could therefore restrict the cells ability to obtain the optimal concentrations of coenzyme Q10, and cells are also dependent on the levels of coenzyme Q10 in order to obtain optimal function of selenium. A small study by Pedersen et al. showed that the Inuits in Greenland who have low incidence of ischemic heart disease have high serum levels of coenzyme Q10, and these are even higher in older people, which was assumed to be a result of traditional food intake [58]. A positive correlation between serum levels of coenzyme Q10 and age and selenium was also reported in males. Hansen et al. from the same author group demonstrated in a later study that high selenium levels ranging from 79 µg/L up to 488 µg/L could be found in the Inuits in Greenland, for the same reason as mentioned above [59].

Selenium and coenzyme Q10 in heart disease

In the literature there is sparse information on studies where patients with heart disease received combined supplementation of selenium and coenzyme Q10. However, Kuklinski et al. conducted a small randomized study consisting of 61 patients with myocardial infarction, using an intervention of selenium and coenzyme Q10 for one year [60]. They reported lower mortality in the group that received active substances; however due to the small group size there was no statistical significance. Witte et al. presented data indicating that supplementation with micronutrients including selenium and coenzyme Q10 could improve cardiac left

ventricular (LV) function according to evaluations made using cardiac magnetic resonance scans [61]. The authors also demonstrated a significant increase in quality of life as evaluated by the Euro-QoL inventory (a European multidisciplinary inventory to evaluate health status), but at the same time no change of the NYHA (New York Heart Association) functional class could be reported. The NYHA functional class grades how a patient with heart disease experiences symptoms of tiredness, breathlessness or chest pain and is graded from I to IV, where IV is symptoms experienced while at rest. However, the study was small, and had a relatively short follow-up period of less than a year.

Leong et al. presented interesting data involving patients undergoing elective coronary artery bypass surgery [62]. Of the 117 participants, 60 received magnesium orotate, lipoic acid, omega-3 fatty acids, selenium and coenzyme Q10 two months prior to surgery and one month after surgery. For the metabolic supplementation group, the authors reported decreased biomarker Troponin T, indicating less cardiac damage, and a shorter postoperative hospital stay.

Selenium and coenzyme Q10 in statin treatment

In patients with ischemic cardiovascular disease, statin treatment is common and well documented in the literature [63–65]. However, it is not uncommon that statin treated patients experience side effects such as myalgia or even myopathy. That the serum level of coenzyme Q10 is decreased during statin treatment is well documented [66]. Statins also inhibit the synthesis of some important selenoproteins [67]. The supplementation of selenium and coenzyme Q10 in patients with myalgia/myopathy has therefore been reported in the literature. Fedacko et al. reported positive effects of the supplementation with coenzyme Q10, but no additional positive effects of the addition of selenium [68]. However, Bogsrud et al. reported that supplementation of selenium and coenzyme Q10 did not affect statin-induced myopathy [69].

The KiSel-10 intervention study

In 2012, we presented an intervention study using selenium and coenzyme Q10 on an elderly municipal population in the south-east of Sweden [69]. This was a prospective double-blind, placebo-controlled study with four years of intervention [70].

The total study population, 443 participants, was randomized into two groups: one given a supplementation of 200 µg/day organic selenium (SelenoPrecise®, Pharma Nord, Denmark), plus 200 mg/day of coenzyme Q10 (Bio-Quinon®, Pharma Nord, Denmark), and the second group given a placebo. All the participants received the supplementation for 48 months according to the schedule. During the intervention time, which was unusually long (median follow-up time 5.2 years), 86 participants suffered all-cause mortality and 129 discontinued the trial, mainly because there were too many tablets to take. Thus, almost 71% completed the trial.

From the evaluation during a follow-up period of 5.2 years, 5.9% (13/221) died a cardiovascular death, meaning death of either cardiac or cerebral origin, in the active treatment group, compared to 12.6% (28/222) in the placebo group (χ^2 : 5.97; p =0.015). The cardiovascular mortality by gender was illustrated in a Kaplan–Meier analysis as seen in Fig. 2.

In a multivariate Cox regression analysis of risk for cardiovascular mortality in the total study population, where adjustments were made for gender, age, hypertension, diabetes, ischemic heart disease, smoking, NYHA functional class III (thus symptoms existing with light exercise), cardiac ejection fraction <40% (meaning cardiac function that is at least moderately impaired as seen on an

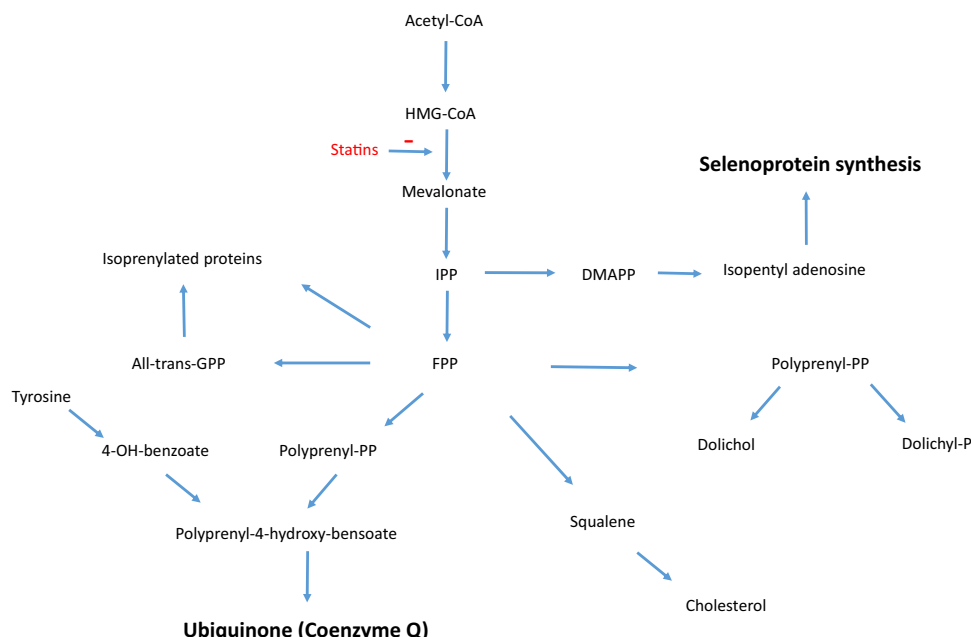


Fig. 1. The major pathways of the synthesis of coenzyme Q10 and of selenoproteins, illustrating also interrelationships between selenium metabolism and coenzyme Q10 synthesis. It is seen that statins may interfere with the synthesis of both selenoproteins and coenzyme Q10. Furthermore, a selenoprotein TrxR1 (cytosolic thioredoxin reductase) is needed for the cell to reduce coenzyme Q10 (ubiquinone) to the active form ubiquinol (not shown in the figure). Note: DMAPP: dimethylallyl pyrophosphate; FPP: farnesyl pyrophosphate; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; IPP: isopentenyl pyrophosphate; polyprenyl-PP: polyprenyl diphosphate.

ultrasound examination), Hb < 120 g/L (meaning anaemia according to the WHO definition), previous thrombosis, treatment with ACE-inhibitors/AII-blockers (meaning pharmacological groups that are one of the main choices in treatment for heart failure), and finally treatment with beta-blockers (one of the groups of choice in heart failure treatment, and in treatment in angina/myocardial infarction), a significant hazard ratio reduction could be seen in those on supplementation with selenium and coenzyme Q10 combined (HR: 0.46; 95%CI 0.24–0.90; $p = 0.02$).

Regarding all-cause mortality, a difference in mortality could be noted between the two groups, but it was not significant (12.7% in the active group, 16.2% in the placebo group (χ^2 : 1.1; $p = 0.29$)).

In order to evaluate a possible effect of the intervention on the cardiac function as evaluated by cardiac ultrasound examination,

a significantly better cardiac function in the active treatment group, as compared to the placebo group could be demonstrated. Finally, an evaluation of the biomarker NT-proBNP (N-terminal fragment of proBNP, a peptide synthesized by the myocardial cells as a response to increased wall tension), was performed. A significantly lower plasma concentration of the biomarkers could be seen in the active treatment group, compared to the placebo group.

The results of this intervention study are encouraging. However, as the study is the first using this combined intervention for such a long intervention time, and the study population was of limited size, it should be regarded as a hypothesis-generating study, stimulating more research in the field of trace elements and oxidative stress.

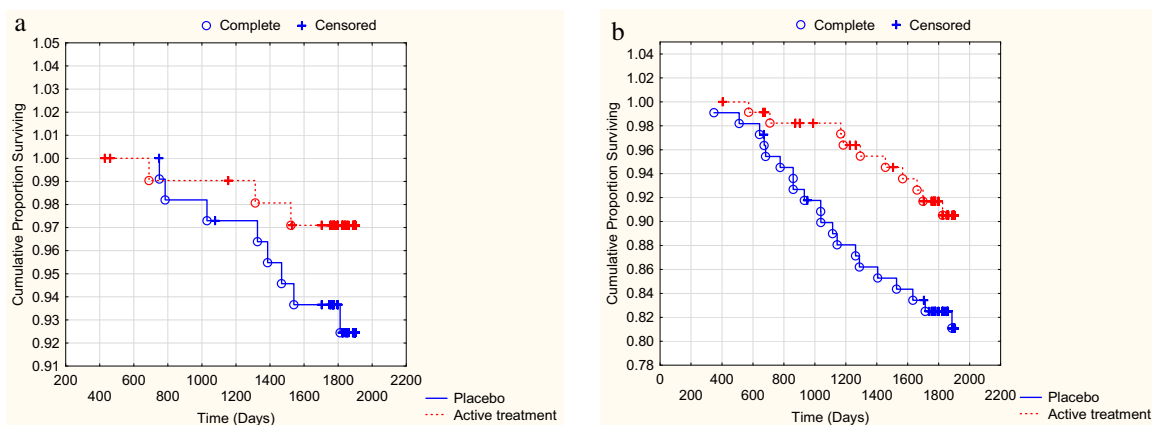


Fig. 2. (a) Kaplan–Meier analysis of cardiovascular mortality in the female study population given intervention of selenium and Q10 combined versus placebo during a follow-up period of 5.2 years. Note: Censored participants were participants who were still alive at the end of the study period or who had died of reasons other than cardiovascular disease. Completed participants comprised those who had died due to cardiovascular disease. (b) Kaplan–Meier analysis of cardiovascular mortality in the male study population given intervention of selenium and Q10 combined versus placebo during a follow-up period of 5.2 years.

Note: Censored participants were participants who were still alive at the end of the study period or who had died of reasons other than cardiovascular disease. Completed participants comprised those who had died due to cardiovascular disease.

Conclusion

Oxidative stress is a condition that the cell is always exposed to, both as age increases, but also in the form of atherosclerotic or inflammatory disease, tumours, or during surgical interventions. Therefore, the body has defences in the form of anti-oxidative substances to correct the imbalance that oxidative stress represents.

Selenium is an essential trace element and one of the major anti-oxidative substances used by the body. It is therefore not surprising that lower levels of selenium in the body could be found during conditions of increased requirements for anti-oxidative capacity. As selenium intake differs around the world, in areas with poor selenium content in the soil, such as Europe, the low selenium intake could lead to a selenium deficiency among the inhabitants. Intervention trials have given interesting but conflicting results. As there is an interrelationship between selenium and coenzyme Q10, and there is a decreasing synthesis of coenzyme Q10 from the age of 20, there might be a theoretical advantage to supplementing both selenium and coenzyme Q10.

This was done in an intervention trial among elderly community inhabitants in Sweden. The result of the trial is intriguing, pointing to a significantly lower cardiovascular mortality, better cardiac function according to cardiac ultrasound examination, and a lower plasma concentration of the biomarker NT-proBNP in those in the active treatment group. However, more research is needed to confirm that combined supplementation of selenium and coenzyme Q10 could improve health partly by countering decreased oxidative stress in the cells.

Conflict of interest

The authors Urban Alehagen and Jan Aaseth has no financial disclosures, and no conflict of interest to report

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