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Cardiovascular mortality and N-terminal-proBNP reduced after combined selenium and coenzyme Q10 supplementation: A 5-year prospective randomized double-blind placebo-controlled trial among elderly Swedish citizens ☆

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ABSTRACT

Background: Selenium and coenzyme Q10 are essential for the cell. Low cardiac contents of selenium and coenzyme Q10 have been shown in patients with cardiomyopathy, but inconsistent results are published on the effect of supplementation of the two components separately. A vital relationship exists between the two substances to obtain optimal function of the cell. However, reports on combined supplements are lacking.
Methods: A 5-year prospective randomized double-blind placebo-controlled trial among Swedish citizens aged 70 to 88 was performed in 443 participants given combined supplementation of selenium and coenzyme Q10 or a placebo. Clinical examinations, echocardiography and biomarker measurements were performed. Participants were monitored every 6th month throughout the intervention.
The cardiac biomarker N-terminal proBNP (NT-proBNP) and echocardiographic changes were monitored and mortalities were registered. End-points of mortality were evaluated by Kaplan–Meier plots and Cox proportional hazard ratios were adjusted for potential confounding factors. Intention-to-treat and per-protocol analyses were applied.
Results: During a follow up time of 5.2 years a significant reduction of cardiovascular mortality was found in the active treatment group vs. the placebo group (5.9% vs. 12.6%; $P=0.015$). NT-proBNP levels were significantly lower in the active group compared with the placebo group (mean values: 214 ng/L vs. 302 ng/L at 48 months; $P=0.014$). In echocardiography a significant better cardiac function score was found in the active supplementation compared to the placebo group ($P=0.03$).
Conclusion: Long-term supplementation of selenium/coenzyme Q10 reduces cardiovascular mortality. The positive effects could also be seen in NT-proBNP levels and on echocardiography.

1. Introduction

Selenium is an essential nutrient required for vital processes within the body such as antioxidant defense, oxidative metabolism, and immune surveillance [1,2]. Dietary selenium is assimilated into selenoproteins, of which 25 are currently known in humans [1]. These include glutathione peroxidase (Gpx), thioredoxin reductase 1 (TrxR1), selenoprotein P, and iodothyronine deiodinases [3]. Dietary supplementation of selenium induces a changed inflammatory response as shown by Goldson et al. [4]. There is a close connection between the selenium content of soil and selenium dietary intake, best exemplified by Keshan disease, an endemic cardiomyopathy found in selenium-deficient areas of inland China [5,6]. The daily intake of this nutrient is regarded as insufficient in many Western European countries and a dietary supplementation of selenium has been suggested [1]. Clark et al. have proposed that selenium affects tumor development [7]. The association between ischemic heart disease and selenium has been reported in several studies [8–10]. Salonen et al. observed a 2.9-fold increased risk of cardiovascular death in patients with low selenium levels [11]. However, the efficacy of selenium supplementation as a single dietary additive has been debated [8–10,12]. Abscence of clinical effects may, in some cases, be explained by short-term intervention periods, coenzyme Q10 deficiency and/or low selenoprotein activity due to concomitant deficiency of isopentenyl Sec-tRNA, a factor necessary for efficient selenoprotein synthesis [13].

Coenzyme Q10 (also termed ubiquinone) is present in all cells of the body and has a central role as an electron carrier in the mitochondrial respiratory chain and in oxidative phosphorylation. Extra-

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mitochondrial coenzyme Q10 is also an efficient lipid soluble antioxidant, protecting against lipid peroxidation. For a normal heart function a steady supply of coenzyme Q10 via the circulatory system or through endogenous synthesis is required. Endogenous synthesis of coenzyme Q10 in the body declines with age indicating a rational for supplementation in the elderly [14]. Already 40 years ago it was reported that 75% of ischemic heart disease patients exhibited low levels of coenzyme Q10 in the plasma and decreasing myocardial levels as the heart disease progressed [12,14].

Low myocardial levels of coenzyme Q10 have been observed in patients with cardiomyopathy [15,16]. Furthermore, non-surviving heart failure patients had lower levels of coenzyme Q10 in the plasma than surviving patients [17]. Dietary supplementation of coenzyme Q10 has been shown to improve the myocardial function and quality of life in patients with ischemic cardiomyopathy [18–20]. The cardio-protective effects of coenzyme Q10 are most likely explained by its antioxidant effect, which requires continuous reduction of ubiquinone and regeneration to the active ubiquinol form. Regeneration of ubiquinol requires selenium in the form of the selenoprotein TrxR1, which contains the unique amino acid selenocysteine (SeC) in its active site. In addition, the synthesis of SeC-containing proteins requires a functional mevalonate pathway, in which coenzyme Q10 is a product [13].

The aim of the present study was to evaluate whether combined supplementation of selenium and coenzyme Q10 in a primary health care cohort would affect the severity of chronic heart failure, all-cause mortality, and cardiovascular mortality. The rationale of this study is underlined by the fact that over 600 references (Pub Med) regarding Q10 and heart disease and over 800 references regarding selenium and heart disease in PubMed. However, most of these references are hypothesis generating basic science indicating the need for a clinical trial.

The secondary objective was to determine whether the intervention could influence cardiac function as evaluated by cardiac natriuretic peptides and echocardiography.

2. Methods

2.1. Study design

The present study was a prospective randomized double-blind placebo-controlled trial.

A rural municipality of 10,300 inhabitants in south-east Sweden was selected for this intervention study. All citizens aged between 70 and 88 years (n = 1320) had previously participated in an epidemiological study and had been continuously followed with medical examinations since 1998. A total of 876 people accepted the invitation to that study. We invited these participants to participate in the present study. In 2003, at the start of this study, however, only 675 of the 876 participants were still alive and not seriously diseased. A total of 443 of the 675 accepted participation in this study which involved taking dietary supplements, and the follow-up program. The first participant was included in January 2003, and the last participant concluded the study in February 2010. All participants were examined by one of three experienced cardiologists. A new clinical history was recorded, a clinical examination was performed, the New York Heart Association functional class (NYHA class) was assessed, and an ECG and Doppler-echocardiographical examination were carried out. Blood pressure was measured with the participant resting in supine position. All participants were supplemented for 48 months, and were re-examined at the end of each six-month period. All-cause and cardiovascular mortalities were registered.

Thus 221 persons were given the active supplement of selenium + coenzyme Q10 (active treatment group), and 222 persons received the placebo supplement (placebo group). The design of the study is illustrated in Fig. 1. Informed consent was obtained from each patient. The study was approved by the Regional Ethical Committee and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The Medical Product Agency declined reviewal of the study protocol since the study was not considered a trial of a medication for a certain disease but rather one of food supplement commodities that are commercially available. The study was registered at clinicaltrials.gov. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.2. Blood samples

Blood samples were collected while the participants were resting in a supine position. Pre-chilled, EDTA-vials were used. The vials were centrifuged at 3000 *g*, +4 °C, and were then frozen at −70 °C. No sample was thawed more than twice.

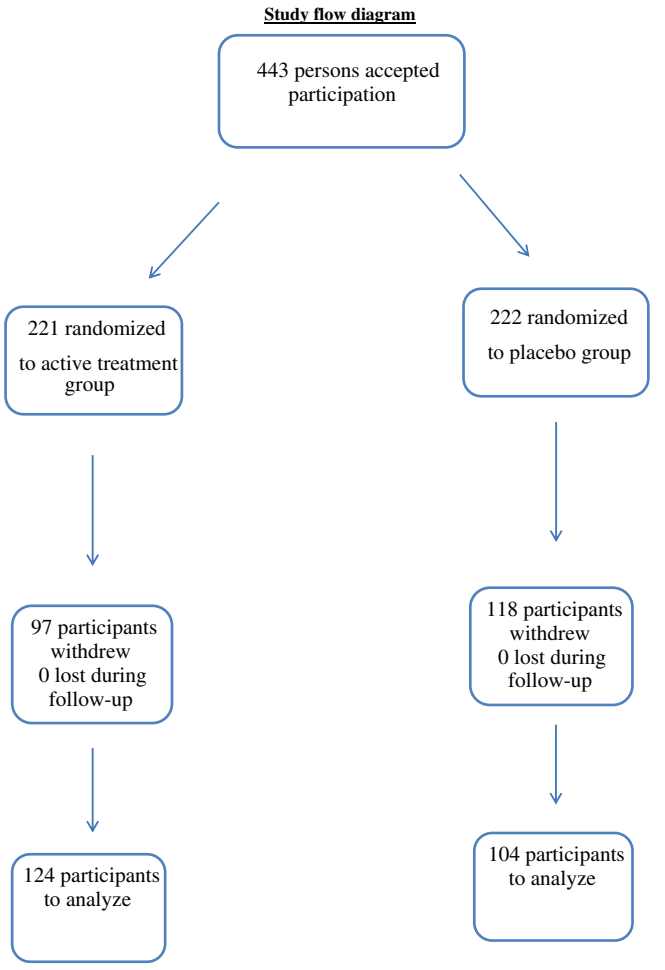

Fig. 1. Flow diagram of the study indicating the two groups; active treatment and placebo.

2.3. NT-proBNP

ProBNP, amino acids 1–76 (NT-proBNP), was measured on the Elecsys 2010 platform (Roche Diagnostics, Mannheim, Germany). The total coefficient of variation was 4.8% at 220 ng/L and 2.1% at 4254 ng/L (n = 70).

2.4. Echocardiography

Doppler echocardiographical examinations were performed with the participant in the left lateral position. The ejection fraction (EF) readings were categorized into four classes with interclass limits placed at 30%, 40% and 50% [22,23]. Normal systolic function was defined as EF ≥ 50%, while severely impaired systolic function was defined as EF < 30%.

2.5. Study intervention

All participants were randomized in blocks of 6 in a double-blind manner and given either a combination of 200 mg/day of coenzyme Q10 capsules (Bio-Quinon 100 mg B.I.D, Pharma Nord, Vejle, Denmark) and 200 μg/day of organic selenium yeast tablets (SelenoPrecise 200 μg, Pharma Nord, Vejle, Denmark), or similar placebo. The study supplementation was taken in addition to regular medication. All study medications (active drug and placebo) not consumed were returned and counted.

The selenium source was a patented selenium yeast, SelenoPrecise®, of a pharmaceutical quality and has a documented batch-to-batch stability in its composition of selenium species [24–26]. Previous results from the Precise pilot studies showed low levels of adverse effects and good absorption [25] in doses up to 300 μg/day. It has been approved as a pharmaceutical drug in Denmark by the Danish Medicines Agency for many years (appr. no. 6233603).

The coenzyme Q10 preparations have shown good absorption and efficacy in previous controlled trials [27,28], and the capsules were identical to medicinal quality capsules registered for heart failure in a European Union Member State (Myoqinon®, authorization no. OGYI 11494-2010).