COENZYME Q10 AND SELENIUM IN HEART FAILURE – A NEW PERSPECTIVE

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Abstract

Optimal treatment of heart failure (HF) is a continuous challenge. Pharmacological progress, interventional or surgical procedures, kinesio-therapeutic rehabilitation have modestly improved the prognosis of HF with reduced ejection fraction (EF), and patients with HF with preserved EF, or those hospitalized for HF regardless of EF still have a high mortality risk^{1,2}. The association to the standard treatment of HF either of CoQ10 (CoQ10) or selenium has been evaluated over the last 30 years in many small and non-statistical powered studies. The recent publication of randomized trials Q-SYMBYO and Kisel-10 renewed interest in these supplements. The article aims to synthesize literature data on the role and mechanism of action of CoQ10 and selenium in HF as well as the results of the published trials and meta-analyses, focusing on the latest.

Keywords: Coenzyme Q10, Selenium, Heart failure

Rezumat

Tratamentul optim al insuficienței cardiace (IC) este o continuă provocare. Progresele farmacologice, procedurile intervenționale sau chirurgicale, reabilitarea kinetoterapeutică au îmbunătățit modest prognosticul IC cu fracție de ejeție (FE) scăzută, iar pacienții cu IC cu FE păstrată sau cei spitalizați pentru IC indiferent de FE continuă să prezinte un risc de mortalitate crescut^(1,2). Asocierea la tratamentul standard al insuficienței cardiace fie a coenzimei Q10 (CoQ10), fie a seleniului a fost evaluată în ultimii 30 ani în numeroase studii mici și fără putere statistică. Publicarea recentă a trialurilor randomizate Q-SYMBYO și Kisel-10 a reînnoit interesul pentru aceste suplimente. Articolul își propune să sintetizeze datele din literatură privind rolul și mecanismul de acțiune a CoQ10 și seleniului în IC, precum și rezultatele trial-urilor și meta-analizelor recent publicate.

Cuvinte cheie: Coenzima Q10, Seleniu, Insuficiență cardiacă.

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Mitochondrial dysfunction and oxidative stress in HF

The current conceptual model of the treatment of HF targets the secondary consequences and peripheral adaptive processes which lead to cardiac remodelling⁽³⁾. Reverse remodelling is currently defined via surrogate markers as improvement of EF, volumes, cardiac mass, and sphericity index⁽⁴⁾. In an article published in 2015, Gheorghiade et al.⁽⁵⁾ highlight the fact that problems in HF are related to the biological anomalies of dysfunctional myocardium: functional alterations in myocytes (mitochondrial, myofibrillar, of signalling pathways or/and calcium utilization), interstitial, microvascular. The authors propose the redefinition of cardiac reverse remodelling as the improvement of myocyte contractility and of cellular and interstitial characteristics. Therefore, it is important to better understand the biological determinants of cardiac dysfunction⁵ and to redirect the therapeutic strategy towards the myocyte, the microcirculation, the interstitium or the metabolic pathways⁽³⁾.

The primary function of the mitochondrion is to generate the main source of myocyte energy stored in the ATP molecule. In addition to this essential role in cellular metabolism, the mitochondrion is also involved in redox homeostasis; fatty acid and

amino acid oxidation; ionic, metabolite and cofactor homeostasis; and heme synthesis⁽⁶⁾. The three mitochondrial subpopulations: subsarcolemmal, intermyofibrillar and perinuclear interact with each other and with the other cellular structures. The interruption of these interactions is enough to reduce the contractile properties and to induce cell death⁽⁷⁾. Given the importance of the structural and functional integrity of the mitochondria, the cell has also developed protection mechanisms such as: the detoxification system of reactive oxygen and aldehyde species, proteases which control the quality of protein synthesis, and the mitochondrial network which controls the number and morphology of mitochondria^(6,7). Reactive oxygen species (free radicals: $\text{OH}^\cdot$, $\text{O}_2^\cdot$ and non-radicals H_2O_2) emerge from multiple cellular sources, but at the myocytic level the main source is represented by the mitochondria^(6,8). Mitochondrial respiration generates superoxide ($\text{O}_2^\cdot$) which is transferred to the free oxygen forming hydrogen peroxide (H_2O_2) which is reduced to the highly reactive free radical hydroxyl ($\text{OH}^\cdot$). Additionally, in the presence of nitric oxide, superoxide may generate peroxynitrite, toxic for the myocytes⁽⁶⁾. The excess of reactive oxygen species also leads to the oxidation of membrane lipids (cellular and intracellular) and of polyunsaturated fatty acids, with the formation of other toxic

products (aldehydes, ketones, alkanes) which diffuse through membranes and amplify the oxidative stress^(6,9). In the “healthy” cell, the antioxidant defence mechanism is present primarily at the mitochondrial level (catalases, peroxidases, aldehyde dehydrogenases), and it is activated concomitantly with the oxidative process.

The negative impact of reactive oxygen species in HF is well-known and consists of fibroblastic activation, matrix metalloproteinase activation, mitochondrial DNA destruction, mitochondrial dysfunction, defective calcium utilisation, and finally determines: decreased contractility, cardiac hypertrophy, maladaptive cardiac remodelling, and cell death^(6,10). It was proved that mitochondrial production of reactive oxygen species in HF is high⁽¹⁰⁾. The source of reactive oxygen species in HF with reduced EF is primarily myocytic⁽¹¹⁾, whereas in HF with preserved EF it is endothelial and microvascular⁽¹²⁾.

In conclusion, the mitochondrion plays an essential role in providing cellular energy majorly contributing to the generation and metabolism of reactive oxygen species. Mitochondrial dysfunction determines myocytic, endothelial and musculoskeletal oxidative stress involved in the pathogenesis of heart failure.

Coenzyme Q10

Coenzyme Q10 (Co Q10) or ubiquinone is present in all nucleated cells. It is a lipophilic molecule consisting of a quinone core to which there are 10 isoprenyl groups attached (hence the name of Q10)⁽¹³⁾. It was discovered in 1957 by Fredrik I. Crane⁽¹⁴⁾. One year later, Karl Folkers (who discovered and isolated vitamins B6 and B12) published the chemical

structure of CoQ10⁽¹⁵⁾ and during the following years he contributed with more than 300 scientific articles regarding its role. At the beginning of the '70s, together with Gian P Littarru, he described the role of CoQ10 deficiency in HF^(16,17,18). In 1978 Peter Mitchell received the Nobel prize in Chemistry for his contribution to the understanding of biological energy transfer, his studies highlighting the essential role of CoQ10⁽¹⁹⁾.

The total level of Q10 in the human body is 1 gram distributed primarily in the heart, liver, kidney and pancreas, organs that use a great amount of energy at rest⁽¹⁵⁾. The major source of CoQ10 is the biosynthesis that involves the mitochondrion, the endoplasmic reticulum and the peroxisomes. An important enzyme involved in biosynthesis is the HMG-CoA reductase. The inhibition of this enzyme by statins leads to CoQ10 depletion and could explain statin myopathy⁽²²⁾. The second source of CoQ10 is exogenous intake. The types of food relatively rich in CoQ10 are meat, fish and some vegetable oils, but intake does not exceed 3-4 mg/day in the case of a normal diet⁽¹⁵⁾.

The main role of CoQ10 is to facilitate ATP production by participating in the electron transport chain in the inner mitochondrial membrane. Therefore, CoQ10 accepts electrons from complex I and II and passes them to complex III. At this level, electrons allow Hydrogen ions to be pumped across the inner mitochondrial membrane, where in the presence of ATP synthase the ADP molecule is converted into ATP. At the same level, reduced CoQ10 (ubiquinol) is converted to its oxidized form (ubiquinone) and resumes its activity⁽¹³⁾. *In vitro* studies proved that CoQ10 also has an important antioxidant role, inhibiting circulating (LDL) and membrane lipid oxidation⁽²⁰⁾, as well as one of improving endothelial function by increasing nitric

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oxide bioavailability and reducing endothelin-1 secretion induced by oxidized LDL⁽²¹⁾ (Figure 1). It was proved that CoQ10 synthesis is low in HF⁽¹³⁾, in statin-treated patients⁽²⁹⁾, and in older people⁽²³⁾.

Coenzyme Q10 in heart failure

Preclinical studies have shown the role of CoQ10 depletion in HF pathogenesis in different experimental animal models^(24,25,26). Proving a direct relationship between the plasma level of CoQ10 in humans and HF is hard to achieve because the determination of ubiquinone/ubiquinol serum level is difficult and non-standardised. Folkers et al.⁽²⁷⁾ proved by endomyocardial biopsy the presence of a significant negative correlation between tissue CoQ10 level and NYHA functional class, as well as an increase in serum and tissue level by oral supplementation. Molyneux et al.⁽²⁸⁾ proved on a group of 236 patients followed 2.6 years on average that the CoQ10 plasma level represents an independent predictor of mortality. A substudy of the CORONA trial⁽²⁹⁾ (1191 patients with ischaemic HF with reduced EF, to which rosuvastatin administration was associated, followed 32 months on average) has shown that older patients with more advanced stages of HF have lower CoQ10 serum levels. Rosuvastatin reduced the CoQ10 serum

level, but this did not prove to be an independent prognostic factor in the multivariate analysis. These mixed results suggest that the CoQ10 plasma level is not an independent prognostic factor but can represent a HF severity marker⁽¹³⁾.

Many studies have been published in the last 30 years regarding CoQ10 supplementation in HF with reduced EF⁽¹³⁾ and only one ongoing randomised trial regarding the reduction of symptoms in HF with preserved EF by using ubiquinol and/or D-ribose⁽³⁰⁾.

Published meta-analyses of the randomised trials regarding CoQ10 administration in HF showed mixed results: most indicated a positive effect on the ejection fraction with or without symptomatic improvement⁽³¹⁻³³⁾. Two systematic reviews have revealed a non-significant trend of mortality reduction⁽³⁴⁾ or the lack of impact on mortality⁽³⁵⁾. All these data analysed studies published until 2012, without including two double-blind randomised trials, published in 2013 - the Ki Sel⁽²³⁾ study and 2014, the Q-SYMBIO⁽³⁶⁾ study respectively.

The Q-SYMBIO trial - (The effect of coenzyme Q10 as adjuvant therapy in chronic heart failure: a randomised, multicentre, double-blind trial focused on SYMptoms, BIOmarker status - BNP, and long-term Outcome) completed and published in JACC: Heart Failure in 2014 was the first trial with an adequate number of patients, followed for an

Figure 1. Mechanism of action and possible benefits of coenzyme Q10

NO = nitric oxide, VS = left ventricle (according to Sharma A. et al^[30])

Figure 2. The role of selenoproteins in the heart

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adequate period of time in order to evaluate CoQ10 efficacy on cardiovascular morbidity and mortality. 420 patients with NYHA class II and III symptoms were enrolled from 17 European, Asian and Australian sites. No cut-off value for EF was specified. Enrolled patients were subsequently randomised for the CoQ10 (BioActive Q10 gold) treatment at a dose of 100 mg three times a day versus placebo, additional to the standard treatment of HF. The study set objectives for two stages: short-term (16 weeks) - change of NYHA functional class, 6-minute walk test and NT-proBNP level; and long-term (two years) - occurrence of major cardiovascular events, respectively. The total daily dose of 300 mg was chosen in order to ensure an increased coenzyme serum level. In previous randomised studies it was proved that an effective CoQ10 plasma level of 2 g/ml can be obtained with doses of 100-200 mg/day⁽³⁶⁾. Also, it was shown that a dose of 100 mg two times a day ensures better absorption than 200 mg once, probably because of the saturation phenomenon and the delay of absorption at intestinal level⁽³⁷⁾. Both groups were similar regarding demographics and standard treatment.

After 16 weeks the NYHA functional class and the 6-minute walk test improved in both groups, without significant differences. The NT-proBNP value was lower in the treated group but statistically non-significant

compared to the placebo group. Coenzyme Q10 serum level increased three times in treated patients.

The 106-week results showed significantly fewer major cardiac events in the CoQ10-treated group (N =30.15%) than the placebo group (N =57.26%), equivalent to a 43% relative risk reduction ($p = 0.005$). As far as the 2-year secondary objectives are concerned, significantly more patients in the treated group changed to an inferior NYHA functional class compared to the placebo group (86 vs 68, $p = 0.028$), cardiovascular mortality was lower in the CoQ10-treated group (18 vs 34, $p = 0.039$), hospitalization for HF was reduced in the treated group (17 vs 31, $p = 0.033$), and general mortality was also reduced in the treated group (21 vs 39, $p = 0.036$). Adverse reactions were reduced more in the CoQ10-treated group compared to placebo, but statistically non-significant (26 vs 41, $p = 0.11$). The subgroup analysis showed that patients who were older, male, NYHA functional class III, who had NT-proBNP higher than 300pg/ml, and $EF \geq 30\%$ benefited most from adding CoQ10 to the treatment. Reduction of endogenous CoQ10 synthesis with age⁽³⁸⁾, malnutrition and the absence of certain micronutrients in HF might explain the benefits mentioned in specific patient categories⁽³⁶⁾.

In general, there are few adverse reactions of the administration of CoQ10. An Italian

study⁽³⁹⁾ mentioned the presence of 38 adverse reactions in 2664 patients (1.5%) consisting predominantly of nausea (N =30) and allergic rash (N =3). Treatment was discontinued by 9 patients.

There are significant drug interactions with antivitamin K as CoQ10 presents structural similarities with vitamin K and interacts with cytochrome P450 enzymes increasing the metabolism of the anticoagulant drug and reducing its effectiveness. Pharmacokinetics of theophylline may be affected through the same mechanism¹³. Statins reduce the CoQ10 serum level⁽²⁹⁾.

Selenium in cardiovascular diseases

Selenium (Se) is a mineral type of chemical element essential to the antioxidant biological mechanism, thyroid hormone metabolism, the functioning of the immune system and, possibly, the prevention of certain cancers⁽⁴⁰⁾. It was discovered in 1817 by Jacob Berzelius and Johan Gahn. It entered the medical field initially for its toxicity (selenosis) to industrial workers and to animals fed with Se-rich cereals. The first data regarding the biological and functional role of Se were published in the '60-70s when its presence was proven in enzyme and protein structures involved in the redox system⁽⁴¹⁾. In the '80s a rapidly progressive endemic form of cardiomyopathy was described, called Keshan disease after the region of China where the cases were identified⁽⁴²⁾. Keshan disease was then also identified in Finland and in New Zealand, in areas with selenium-poor soil, this being the major predisposing factor which amplifies the virulence and cardiotoxicity of Coxsackie B virus⁽⁴³⁾.

The major source of selenium in the body consists of nut, mushroom and cereal

exogenous intake. Intensification methods of agricultural production led to selenium-deficient soil and consequently to its deficiency in humans and animals, which caused Finland to supplement fertilizers with selenium⁽⁴⁴⁾.

Selenium plays its role through its incorporation in at least 25 selenoproteins⁽⁴⁰⁾. The most important are: glutathione peroxidase family, involved in the neutralisation of reactive oxygen species, thioredoxin family involved in myocardial remodelling in oxidative stress, iodothyronine deiodinase family involved in thyroid hormone regulation, and also selenoproteins R, K and S involved in the regulation of ischaemia-reperfusion, atherogenesis and myocyte hypertrophy process⁽⁴⁰⁾ (Figure 2). Although there is much *in vitro* and preclinical evidence of the biological role of Se, meta-analyses of trials which evaluated prophylactic selenium supplementation did not identify any reduction in mortality and/or non-fatal cardiovascular events⁽⁴⁰⁾. A recently published randomised trial proved the benefit of perioperative administration of selenium in cardiac surgeries⁽⁴⁷⁾. Given the mixed observational reports and long-term data of NHANES study, a "U"-shaped relationship was proposed between Se serum level and cardiovascular morbidity/mortality, optimal serum value being 130 µg/L^(45,46). There are no randomised trials regarding selenium efficacy in HF, except Keshan disease and co-administration with CoQ10, the Ki Sel study, presented below.

Ki Sel trial

The rationale behind combined administration of CoQ10 and Se stemmed from the existing evidence regarding the

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essential role of CoQ10 (over 600 references mentioned in PubMed) and selenium (over 800 references mentioned in PubMed) in cellular metabolism and from the vital interrelation between the two elements (ubiquinol regeneration requires the presence of selenium in the form of selenocysteine-containing thioredoxin, and selenocysteine synthesis requires the presence of CoQ10)⁽²³⁾. The study was conducted in the Swedish city of Kisa, it was prospective, randomised, double-blind, it took place between 2003 and 2010, and was published by Alehagen et al. in The International Journal of Cardiology in 2012⁽²³⁾. The primary objective was to evaluate the benefit of the co-administration of selenium (SelenoPrecise, 200 g/day) and CoQ10 (BioQuinone 100 mg x2/day) regarding HF severity, cardiovascular and general mortality in a cohort of elderly patients (70-88 years) who also participated in other epidemiological studies and had been under surveillance since 1998. The secondary objective was to determine the influence of the intervention on NT-proBNP. 443 patients were randomised for the active treatment and placebo arms. Demographics of the two groups were similar. Patients were followed for 5.2 years. 215 patients left the study (43.9% of the active arm and 53.2% of the placebo arm), the main reasons being the great number of pills for long-term

administration and the difficulty in accessing the evaluation site due to old age. Adverse reactions were non-significant (7 patients in the active group and 4 in the placebo group had diarrhoea). The study proved a significant decrease in cardiovascular mortality in the treated group vs placebo (5.9% vs 12.6%, $p = 0.015$). General mortality was not influenced ($p = 0.29$). The echocardiographic analysis showed a significantly better EF in the active group vs placebo ($p = 0.07$) despite the fact that many patients with low EF in the placebo group left the trial. NT-proBNP values recorded significant differences at 24 months, as they had higher values in the placebo group ($p = 0.048$), marked at 48 months ($p = 0.014$). Participants who remained in the Ki Sel trial⁽²³⁾ ($n=228$) were re-evaluated 8 years after the end of the study, period during which CoQ10 and selenium administration was interrupted. Results published by Alehagen et al.⁽⁴⁸⁾ proved a significant decrease in cardiovascular mortality in the patient group previously treated with CoQ10 and selenium compared to placebo (28.1% vs 38.7%, $p < 0.001$). In the subgroup analysis patients with $FE < 40\%$ (HR 0.56, $p=0.03$), ischaemic cardiac disease (HR 0.56, $p=0.03$), hypertension (HR 0.6, $p=0.03$) or diabetes mellitus (HR 0.59, $p=0.003$) had the greatest benefit. A decrease in cardiovascular mortality 12

years after the active intervention for 4 years with CoQ10 and selenium proves the persistent positive effects of the combination. The explanation proposed by the authors would be that selenium and coenzyme Q10 inhibit the pathogenesis of some irreversible structural alterations precursory to cardiovascular events.

Conclusions

The approach of a new therapeutic strategy in HF that targets cellular metabolism in the myocardial structure currently represents a necessity determined by the high prevalence, the poor prognosis despite compliance with management recommendations of current guidelines and the continuous ageing of the population which leads to an increasing incidence of this disease. Cellular oxidative processes that are mostly mitochondrial are proven causes of myocyte dysfunction. Coenzyme Q10 and selenium are key factors in the production of cellular energy stored in the ATP molecule and in the oxidative balance. Based on these preclinical data, many studies that evaluated the separate administration of the two compounds were published. A particular aspect was represented by the diversity of the products that were administered (e.g. ubiquinone or ubiquinol, in form of tablets, chewable, dissolving tablets, oily solutions; organic or inorganic selenium, orally or intravenously) some of them later proving to be underdosed. The results of these small and heterogeneous studies were mixed, as were the results of the meta-analyses conducted, hence the lack of European and American heart failure management guideline recommendations to initiate treatment with nutritional supplements. There is a need for large studies, adequately

designed, with patented products to prove the benefit of this therapeutic approach. Until then, we cannot ignore the results of the two recent studies mentioned (Q SYMBIO and Ki Sel) that have proven the benefit of long-term administration of CoQ10 and CoQ10 plus selenium, respectively, regarding cardiovascular mortality and HF severity, especially in elderly population. Adverse reactions were few and non-significant, and notable drug interactions were those of CoQ10 with antivitamins K, whose efficacy is reduced. These data support the idea that the decision to add or maintain coenzyme Q10 and selenium to the standard treatment of HF could also depend on the patient's option, after his/her informing.

The knowledge and customized application of clinical practice guideline recommendations is mandatory but, to the same extent it is important to keep an open mind to the alternatives, on condition that the "primum non nocere" principle be observed, and that the relationship with the patient be based on informed collaboration.

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