Research Communication

Association between serum level of ubiquinol and NT-proBNP, a marker for chronic heart failure, in healthy elderly subjects

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Abstract

Ubiquinone and ubiquinol represent the oxidized and reduced forms of Coenzyme Q10 (CoQ10). CoQ10 is present in membranes of almost all human tissues and organs, with highest concentration in the heart. In patients with heart failure, serum levels of the N-terminal pro-brain natriuretic peptide (NT-proBNP) are an indicator of disease severity. Here, we investigated the relationship between serum levels of CoQ10 and NT-proBNP in healthy volunteers of an elderly study population (mean age 52 years, n = 871). We found a negative association between serum levels of ubiquinol and NT-proBNP (P<0.001). Accordingly, the CoQ10 redox state (% oxidized form of CoQ10) is positively associated with serum NT-proBNP level (P<0.001). Compared to patients who survived a myocardial infarction (n = 21), healthy subjects have lower NT-proBNP level (500.39 ± 631.28 pg/ml vs. 76.90 ± 120.27 pg/ml, P<0.001), higher ubiquinol serum level (0.43 ± 0.19 μmol/L vs. 0.71 ± 0.32 μmol/L; P<0.001), and a lower CoQ10 redox state (27.6 ± 13.8% vs. 17.6 ± 10.1%; P<0.001). Interestingly, ubiquinol supplementation (150 mg/day; 14 day; n = 53) slightly reduces the expression of CLCN6, a gene related to NT-proBNP level. In summary, higher serum levels of ubiquinol are associated with lower serum NT-proBNP levels in healthy elderly subjects. However, to what extent a high serum level of ubiquinol is a protective factor for heart failure remains to be elucidated in prospective studies.

Keywords: CoQ10 redox state; oxidative stress; antioxidants; NT-proBNP; heart failure

1. Introduction

Coenzyme Q10 (CoQ10) is a lipophilic redox molecule which is present in membranes of almost all tissues and organs of the human body, with highest concentrations in the heart [1,2]. Ubiquinone and ubiquinol (Q10H2) represent the oxidized and reduced forms of CoQ10. It is synthesized within the mitochondrial inner membrane and is essential for the respiratory transport chain. As an antioxidant in membranes, CoQ10 is important for the maintenance of the cellular redox homeostasis [3]. Furthermore, CoQ10 is necessary for pyrimidine biosynthesis and acts as a cofactor of uncoupling proteins [4]. CoQ10 has also been identified as a modulator of gene expression [5–7], inflammatory processes [8–10], and apoptosis [11,12]. Ubiquinol serves as a regenerator of other lipid soluble antioxidants [13]. There is also evidence that ubiquinol is an important inhibitor of oxidative damage caused by high amounts of
reactive oxygen species (ROS), a condition known as oxidative stress [14,15]. As shown in several studies, the redox state of CoQ10 is an indicator of increased oxidative stress [16–18]. In line with this, the reduced form of CoQ10 is decreased in older organisms [2,19] and plays a crucial role in several diseases such as coronary heart disease, hyperlipidemia, or liver disease [16,17,20].

The N-terminal pro-brain natriuretic peptide (NT-proBNP) is synthesized in the heart [21,22]. High blood concentration of NT-proBNP is strongly associated with cardiac dysfunction and is a useful biomarker for the diagnosis of heart failure [23–26]. Increasing values of NT-proBNP are also associated with an elevated risk of severe cardiovascular events, stroke, or sudden death [27,28]. Moreover, patients suffering from heart failure profit by a consecutive down-regulation of NT-proBNP levels [24]. The regulation of NT-proBNP at transcriptional level seems to be complex and is not fully understood so far. Recently, a genome-wide association analysis identified genetic variants in a cluster of four genes (MTTHFR, CLCN6, NPPA, and NPPB) which are related to NT-proBNP levels [29]. Here, we investigated the relationship between CoQ10 status and NT-proBNP in healthy elderly subjects. In addition, the effect of ubiquinol supplementation on the expression of the genes MTTHFR, CLCN6, NPPA, and NPPB was explored.

2. Methods

2.1. Basic Study Population

The study population is part of the PopGen control cohort [30]. The study population consisted of 409 healthy blood donors between 19 and 62 years old and 483 study subjects aged between 48 and 75 years randomly recruited via registry office of Kiel, Germany. A total of 52.2% were males. All study participants were phenotyped with respect to anthropometric, cardiovascular, and metabolic traits in a standardized fashion (details below). Blood samples were taken after an overnight fast and immediately centrifuged. Serum samples were stored at −80 °C. The participants had no history of gastrointestinal, hepatic, or renal diseases, maintained usual nutrition habits, and were non-smokers or occasional smokers. The study was approved by the ethics committee of the Medical Faculty of Kiel University and was consistent with the Helsinki Declaration. All volunteers gave informed consent.

2.2. Intervention Study (Gene Expression)

Sample characteristics of subjects and study design for intervention study have been described lately [31]. Briefly: 53 healthy male volunteers aged between 21 and 48 years received 150 mg/day of the reduced form of CoQ10 (Q10H2, ubiquinol, KANEKA Corporation, Japan) in form of three capsules with each principal meal for 14 days. Fasting blood samples were taken before (T0) and after (T14) supplementation. The participants had an average body mass index (BMI) of 24.1 ± 2.5 kg/m², no history of gastrointestinal, hepatic, cardiovascular, or renal diseases, a habit of non- or occasional smoking and maintenance of usual nutrition habits. The study was approved by the ethics committee of the Medical Faculty of Kiel University, Germany, and was conform to Helsinki Declaration. All volunteers gave written informed consent.

2.3. CoQ10 and NT-proBNP Analysis

The analysis of ubiquinol-10 and ubiquinone-10 was based on the method of high-pressure liquid chromatography (HPLC) with electrochemical detection as described elsewhere [32]. Briefly, as internal standards, 56 pmol of ubiquinol-9 plus 9 pmol ubiquinone-9 (Sigma–Aldrich, Taufkirchen, Germany) in 50 μl ethanol was added to a 50 μl serum aliquot. After hexane extraction (500 μl hexane) and centrifugation (5 min, 1,000g, 4 °C), the separated hexane phase was evaporated to dryness under a stream of argon and the dry residue was re-dissolved in 50 μl ethanol for injection into the HPLC system. The analytical column was a Prontosil 120-3-C18-SH PEEK column (Bischoff, Leoberg, Germany). The detection system consisted of a Coulochem II electrochemical detector (ESA, Bedford, MA) connected with a Model 5021A conditioning cell and a Model 5011A analytical cell. NT-proBNP was determined with an Elecsys 20.10 bench top analyzer (Roche Diagnostics, Meylan, France) with proBNP reagent pack (Roche Diagnostics).

2.4. Clinical Parameters, Metabolic Parameters, and Gene Expression

Blood pressure measurements were obtained while the subject was in a seated position, using a standard manual sphygmomanometer. A fasting venous blood sample was obtained from all study participants and analyzed following standard procedures. Briefly, blood glucose was analyzed using a hexokinase method (Gluco-quant, Roche Diagnostics, Mannheim, Germany). Cholesterol and triacylglycerol concentrations were measured enzymatically by hydrolyzing cholesterol ester and triacylglycerol to cholesterol and glycerol, respectively. HDL cholesterol (HDL-C) was measured in the supernatant after precipitation of lipoproteins (kits and standards by Konelab Corporation, Espoo, Finland). Microarray experiments using the Affymetrix human genome U133 plus 2.0 GeneChip® were performed as previously described [6] with RNA samples from CD14-positive monocytes obtained from three volunteers before (T0) and after (T14) supplementation with ubiquinol [31].

2.5. Anthropometric Measurements

Body weight was measured in underwear on a manual scale to the nearest 100 g (Seca, Hamburg, Germany). Height was measured without shoes on a stadiometer (Seca, Hamburg, Germany) to the nearest 0.5 cm.

2.6. Diagnosis of Myocardial Infarction

Participants were asked by a trained study nurse in a standardized interview whether they had a myocardial infarction diagnosed by a physician. Self-reported myocardial infarctions were validated by a cardiologist based on EKG data.

2.7. Statistics

Statistical analyses were performed with SPSS (Statistical Package for the Social Sciences) 20.0 software (SPSS GmbH Software, Germany).
München, Germany). Before statistical analysis, normal distribution of the parameters was tested. Gender-related differences in anthropometric and metabolic parameters and differences between healthy subjects and heart cases were analyzed using a nonparametric Mann–Whitney U-test. The relationships between NT-proBNP levels and age and CoQ10 status, respectively, were assessed with a nonparametric Spearman correlation coefficient. The level of statistical significance was set at $P < 0.05$.

### 3. Results

#### 3.1. Characterization of Study Population

Means of age, nutritional status, CoQ10 status, NT-proBNP, and metabolic and cardiovascular risk factors of our study population are given in Table 1. Study subjects were slightly overweight with a mean age of 52.1 years (range 19–75 years) whereas the major part of the population (>60%) was older than 50 years (Fig. 1). On average, serum levels of CoQ10 and NT-proBNP were in a normal range. Except from borderline values for total cholesterol, components of metabolic syndrome were below the thresholds defined by the Adult Treatment Panel III (ATPIII). Gender-stratified analyses revealed significant differences between males and females. Compared to women, men had higher BMI and blood pressure, higher serum levels of CoQ10, ubiquinol, triglycerides, NT-proBNP as well as glucose and lower CoQ10 redox state (% oxidized form in total) and serum HDL-cholesterol levels, respectively.

There is strong evidence that CoQ10 is related to total cholesterol [33–36]. To verify our CoQ10 measurements, we conducted a correlation analysis with total CoQ10 and total cholesterol. As shown in Fig. 2, there was a strong relationship between total levels of CoQ10 and cholesterol in the whole study population as well as in gender-specific subgroups. Just as total CoQ10 levels, the ratio of total CoQ10/cholesterol was higher in men than in women (Table 1).

To examine whether there are metabolic differences between healthy volunteers and subjects who survived myocardial infarction, the study collective was stratified into respective sub-groups (Table 2). Patients who have been diagnosed with myocardial infarction were significantly older than healthy volunteers. Of note, except from cholesterol, there were no differences between healthy subjects and heart patients regarding the parameter of the metabolic syndrome. Interestingly, cholesterol levels were higher in healthy volunteers compared to subjects diagnosed with myocardial infarction.

### Table 1

*Characterization of study population (n = 892)*

<table>
<thead>
<tr>
<th></th>
<th>All (n = 892)</th>
<th>Males (n = 466)</th>
<th>Females (n = 426)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.1 ± 14.2</td>
<td>52.3 ± 14.0</td>
<td>51.9 ± 14.5</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.4 ± 4.5</td>
<td>26.6 ± 3.8</td>
<td>26.1 ± 5.1**</td>
</tr>
<tr>
<td>CoQ10 (µg/ml)</td>
<td>0.86 ± 0.35</td>
<td>0.90 ± 0.37</td>
<td>0.80 ± 0.32***</td>
</tr>
<tr>
<td>Ubiquinol (µg/ml)</td>
<td>0.71 ± 0.32</td>
<td>0.76 ± 0.34</td>
<td>0.65 ± 0.29***</td>
</tr>
<tr>
<td>Ubiquinone (µg/ml)</td>
<td>0.14 ± 0.09</td>
<td>0.14 ± 0.09</td>
<td>0.14 ± 0.09</td>
</tr>
<tr>
<td>CoQ10 redox state (%)</td>
<td>17.7 ± 10.0</td>
<td>16.6 ± 9.4</td>
<td>18.7 ± 10.2***</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>86.9 ± 164.9</td>
<td>78.5 ± 186.1</td>
<td>96.1 ± 137.7***</td>
</tr>
<tr>
<td>systolic BP (mm Hg)</td>
<td>134 ± 17</td>
<td>137 ± 17</td>
<td>130 ± 16***</td>
</tr>
<tr>
<td>diastolic BP (mm Hg)</td>
<td>80 ± 10</td>
<td>82 ± 9</td>
<td>78 ± 9***</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>128.6 ± 78.3</td>
<td>142.1 ± 88.2</td>
<td>114.0 ± 63.0***</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>209.5 ± 41.7</td>
<td>206.9 ± 43.2</td>
<td>212.4 ± 39.8***</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>65.8 ± 18.1</td>
<td>58.1 ± 14.6</td>
<td>74.2 ± 17.9***</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>89.3 ± 14.6</td>
<td>91.7 ± 16.2</td>
<td>86.6 ± 12.0***</td>
</tr>
<tr>
<td>CoQ10/Cholesterol</td>
<td>0.16 ± 0.06</td>
<td>0.17 ± 0.05</td>
<td>0.15 ± 0.05</td>
</tr>
</tbody>
</table>

CoQ10 = Coenzyme Q10; CoQ10 redox state = % oxidized CoQ10 in total; NT-proBNP = N-terminal pro-brain natriuretic peptide; BP = blood pressure; HDL = high density lipoprotein.

Data are presented as mean ± SD; **$P < 0.01$; ***$P < 0.001$ significant differences between sexes, Mann–Whitney U-test.
3.2. CoQ10 Status and NT-proBNP Levels in Healthy Subjects Compared to Patients Who Survived Myocardial Infarction

High serum concentration of NT-proBNP is strongly associated with cardiac dysfunction [23–26]. Therefore, we investigated whether healthy subjects differ from patients who suffered from myocardial infarction regarding NT-proBNP levels and CoQ10 status. As shown in Fig. 3A, healthy probands had considerably lower NT-proBNP levels compared to patients who survived myocardial infarction (500.4 ± 631.3 pg/ml vs. 76.9 ± 120.3 pg/ml; P < 0.001). Interestingly, we found higher levels of total CoQ10 (Fig. 3B; 0.86 ± 0.35 μg/ml vs. 0.69 ± 0.29 μg/ml; P < 0.05) and ubiquinol (Fig. 3C; 0.71 ± 0.32 μg/ml vs. 0.43 ± 0.19 μg/ml; P < 0.001) in healthy subjects compared to heart attack patients. The CoQ10 redox state expressed as percent oxidized in total was lower in healthy persons than in patients (Fig. 3D; 17.4 ± 9.7% vs. 27.6 ± 13.8%; P < 0.01).

3.3. Relationship Between CoQ10 Status and NT-proBNP in Healthy Elderly Volunteers

To investigate the relationship between CoQ10 status and NT-proBNP in healthy probands, subjects who have been diagnosed with myocardial infarction were excluded. As shown in Table 3, there was a positive correlation between NT-proBNP levels and age (P < 0.001). Serum CoQ10 level was negatively
Differences between healthy study subjects (n = 871) and subjects who suffered from heart attack (n = 21) regarding NT-proBNP levels (A), total coenzyme Q₁₀ level (B), ubiquinol level (C), and coenzyme Q₁₀ redox state (% oxidized in total, D). Bar graphs are presented as mean ± SD.

**FIG 3**

**TABLE 3** Spearman’s correlation coefficients from bivariate correlation between NT-proBNP level and Coenzyme Q₁₀ status in healthy elderly subjects

<table>
<thead>
<tr>
<th></th>
<th>All (n = 871)</th>
<th>Males (n = 450)</th>
<th>Females (n = 421)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.353***</td>
<td>0.404***</td>
<td>0.330***</td>
</tr>
<tr>
<td>Coenzyme Q₁₀ (µg/ml)</td>
<td>−0.073*</td>
<td>−0.022</td>
<td>−0.016</td>
</tr>
<tr>
<td>Ubiquinol (µg/ml)</td>
<td>−0.130***</td>
<td>−0.048</td>
<td>−0.093</td>
</tr>
<tr>
<td>Ubiquinone (µg/ml)</td>
<td>0.124**</td>
<td>0.101*</td>
<td>0.163**</td>
</tr>
<tr>
<td>Coenzyme Q₁₀ redox state (%)</td>
<td>0.228***</td>
<td>0.186***</td>
<td>0.177***</td>
</tr>
<tr>
<td>Coenzyme Q₁₀/cholesterol</td>
<td>−0.116**</td>
<td>−0.002</td>
<td>−0.091</td>
</tr>
</tbody>
</table>

NT-proBNP = N-terminal pro-brain natriuretic peptide; CoQ₁₀ redox state = % oxidized CoQ₁₀ in total.
*P < 0.05, **P < 0.01, ***P < 0.001.
related to NT-proBNP level ($P < 0.05$) in the whole study population. This negative association became more evident when the reduced form of CoQ10, ubiquinol, was correlated with NT-proBNP level ($P < 0.001$). Accordingly, ubiquinone level ($P < 0.01$) and CoQ10 redox state ($P < 0.001$) were positively associated toward NT-proBNP level, respectively. After stratification for gender, NT-proBNP’s positive associations remained for ubiquinone and CoQ10 redox state in both females and males. However, no significant correlations between NT-proBNP and CoQ10 or ubiquinol were found in the gender-specific subgroups. The positive association between levels of ubiquinone and NT-proBNP was stronger in women compared to men.

As NT-proBNP is a marker for heart insufficiency, we analyzed associations between CoQ10 status and NT-proBNP in (i) subjects with marker levels >100/150 pg/ml (m/f) and (ii) in patients who survived myocardial infarction. In probands with increased NT-proBNP levels no significant correlations were found between CoQ10 status and NT-proBNP whereas in patients who suffered from myocardial infarction, levels of ubiquinone and NT-proBNP correlated positively ($P < 0.05$; data not shown).

### 3.4. Effect of Ubiquinol Supplementation on the Expression of Genes that Are Related to NT-proBNP Level

Finally, we investigated the effect of CoQ10 supplementation on the expression of genes which are related to the level of NT-proBNP: $MTHFR-CLCN6-NPPA-NPPB$. For this purpose, we reanalyzed our human intervention study regarding gene expression in CD14-positive monocytes, obtained from subjects supplemented with ubiquinol [31]. After 14 days of supplementation with 150 mg/day ubiquinol, the mRNA steady-state level of $CLCN6$ was reduced by a factor of 1.37 whereas the mRNA levels of $MTHFR$, $NPPA$, and $NPPB$ showed no changes (Fig. 4).

### 4. Discussion

#### 4.1. Study Population

In this study, levels of total CoQ10 and total cholesterol were strongly correlated. This has been shown by several researchers [33–36]. With a mean age of 52 years our probands represent an elderly study population. We found gender specific differences regarding serum levels of total CoQ10 and ubiquinol. This is affirmed by other groups [34,37,38]. The CoQ10 redox state (%oxidized in total) was relatively high in our elderly study sample. This is in agreement with other studies showing that the CoQ10 redox state increases in ageing humans and animals [19,39]. Therefore, we conclude that the elevated values for CoQ10 redox state rely on the high percentage of elderly study subjects in our study population.

Interestingly, except from total cholesterol, the single features of the metabolic syndrome did not differ between subjects who have been diagnosed with myocardial infarction and...
healthy controls. Total cholesterol levels were higher in healthy volunteers compared to heart patients. However, this is in line with findings from others who reported that lower serum cholesterol was independently associated with total mortality in patients with chronic heart failure [35,40]. Because total CoQ10 concentration strongly correlates with total cholesterol, the higher values of cholesterol in healthy volunteers are accompanied by higher CoQ10 levels and hence to be in charge of the protective effects regarding myocardial infarction.

4.2. CoQ10 Status and NT-proBNP in Healthy Persons

In healthy elderly subjects, the knowledge about the relationship between CoQ10 status and the heart disease marker NT-proBNP is rather limited. In general, pro-BNP is strongly associated with cardiac functions and is a powerful predictor of many cardiovascular outcomes, especially heart failure [27]. Increasing values of NT-proBNP are associated with an elevated risk of severe cardiovascular events, stroke, or sudden death [27,28]. Molyneux et al. described a negative correlation between total CoQ10 serum level and NT-proBNP levels in patients with severe heart failure [35]. This is in line with our findings in healthy volunteers. Additionally, we found a negative correlation between the reduced form of CoQ10, ubiquinol, and NT-proBNP level in our study sample. Accordingly, CoQ10’s oxidized form, ubiquinone, as well as CoQ10 redox state expressed as the oxidized percentage in total CoQ10, showed positive correlations toward NT-proBNP level. In patients who suffered from myocardial infarction, solely ubiquinone was positively correlated with NT-proBNP while in subjects with elevated NT-proBNP level no associations toward CoQ10 status were found. Taken together, within the normal range of NT-proBNP, serum ubiquinol levels are negatively associated with NT-proBNP levels in our study sample. Therefore, we propose that a high serum concentration of ubiquinol might be a protective factor for heart failure in healthy elderly persons. Though, this has to be further investigated in prospective studies.

4.3. CoQ10 Status and NT-proBNP in Patients Who Suffered from Heart Failure

For a physiological heart function, a steady supply of CoQ10 is needed to cover the high energy requirements of cardiac muscle cells. However, it has been reported that CoQ10 content in human heart showed the highest levels at around 20 years of age and after which it decreased to nearly 40% of the highest peak level at the age of around 80 years [2]. Also, in patients suffering from heart failure a myocardial depletion of CoQ10 has been demonstrated whereby the severity of the deficiency has been found to correlate with the severity of symptoms [41]. This is underlined by others who found significantly lower plasma levels of CoQ10 in patients with cardiomyopathy compared to healthy controls [35,42]. In line with these findings, we found that patients who suffered from myocardial infarction had significantly higher NT-proBNP values, lower total CoQ10 levels, lower levels of ubiquinol, and a higher CoQ10 redox state. These findings underline the hypothesis of increased oxidative stress expressed by CoQ10 redox state in patients with heart failure [17,20]. Therefore, it might be recommendable for patients suffering from heart disease to improve their redox state by supplementation of ubiquinol.

4.4. Effects of Ubiquinol Supplementation on NT-proBNP Levels, Symptoms of Heart Failure, and Gene Expression

Several researchers reported on beneficial effects from CoQ10 supplementation in patients with heart failure [43–46]. In 2003, Mortensen et al. initiated Q-SYMBIO as an international, randomized, double-blind multicenter intervention study with CoQ10 supplementation in patients with chronic heart failure focusing on symptoms, biomarker (e.g., NT-proBNP) and long-term outcomes [47]. Initially, they found that supplemented CoQ10 (300 mg/day) reduced levels of NT-proBNP with a mean reduction of 20% after 16 weeks of intervention in the study group whereas probands of the placebo group showed an increase of NT-proBNP level of about 12%. However, the respective between-group changes from baseline values to week 16 were not significant [48]. After 2 years into the trial, NT-proBNP level was more than halved in both study groups but without significant differences between groups. The authors declared these results with the death of the probands with the highest NT-proBNP levels, respectively [48]. But finally, Mortensen et al. were able to show that long-term CoQ10 treatment reduced major adverse cardiovascular events, cardiovascular mortality, all-cause mortality, and hospitalizations in patients with moderate to severe heart failure without any side effects [48]. Similar results were shown in a Swedish population among elderly study subjects where the supplemental effect of combined selenium and CoQ10 on NT-proBNP was tested in a placebo-controlled trial. After 48 months of supplementation, study subjects had significantly lower levels of NT-proBNP compared to placebo-group [49,50]. However, it was noticed that the effect of supplementation varied depending on the basic level of NT-proBNP; only subjects with mild to moderate increased NT-proBNP levels had benefit from supplementation [50].

Here, we reanalyzed our human study investigating the effect of a 14-day ubiquinol-supplementation on gene expression patterns [31]. We analyzed MTHFR, CLCN6, NPPA, and NPPB because variants in these genes are associated with serum NT-proBNP levels in humans [29]. Interestingly, one SNP in the CLCN6 gene was associated with NT-proBNP independently from the others genes’ variants. Additionally, this SNP was the best predictor of the NT-proBNP level compared to the other genes [29]. Here, we found that ubiquinol supplementation reduces the CLCN6 mRNA by a factor of 1.37. The mRNAs of MTHFR, NPPA, and NPPB showed no changes. These findings provide preliminary evidence that ubiquinol reduces NT-proBNP levels via decreased expression of the CLCN6 gene.

5. Conclusion

In healthy elderly subjects, we found a negative correlation between serum level of ubiquinol and NT-proBNP, a biomarker for chronic heart failure. This might be an indication...
that higher level of ubiquinol is a protective factor for heart failure. Though, this hypothesis remains to be tested in prospective studies.

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References


