Plasma Ubiquinone Status and Response to Six-Month Supplementation Combined with Multivitamins in Healthy Elderly Women – Results of a Randomized, Double-Blind, Placebo-Controlled Study

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Abstract: The aim of this study was to evaluate the serum coenzyme Q10 concentrations of healthy elderly women before and after supplementation with coenzyme Q10 combined with multivitamins, selenium, and magnesium. In a randomized double-blind design, 220 free-living women aged 60 years and older were included. Median serum coenzyme Q10 concentration at baseline was 0.99 µmol/L (5–95 percentiles: 0.54–1.68) and cholesterol adjusted concentration was 0.16 (5–95 percentiles: 0.09–0.26) mmol/mol cholesterol. No significant correlations were found between Q10 levels and body mass index (BMI) or age. Q10 concentrations were not significantly different between smoking and nonsmoking women, nor between women with statin therapy and without. Furthermore no differences were seen between hyperlipidemic and normolipidemic subjects. Cholesterol-adjusted Q10 levels were positively correlated to lipid-adjusted serum tocopherol levels and negatively associated to serum beta-carotene. No significant correlation existed between adjusted Q10 levels and plasma selenium. Results of the food diaries showed a significant but weak correlation to meat and meat products and to alcohol intake.

At baseline, Q10 levels did not differ between supplemented and control group. After six months, adjusted serum concentrations of the supplemented and the control group were significantly increased by 106% and 31%, respectively. In the supplemented group the change was inversely associated with the baseline concentration. A six-month supplementation with coenzyme Q10, vitamins, and selenium raises the blood concentration of coenzyme Q10 even in relatively well-nourished elderly women.

Key words: Coenzyme Q10, ubiquinol, ubiquinone, antioxidants, supplementation, elderly, women, HMG-CoA reductase inhibitors, statins

Introduction

In addition to its role as a coenzyme for the inner mitochondrial enzyme complexes involved in oxidative phosphorylation, coenzyme Q also has antioxidant properties. It has been assumed that ubiquinol can act as an antioxidant by direct and indirect mechanisms. As a chain-breaking antioxidant it is able to reduce peroxyl and alcoxyl radicals; on the other hand, in a redox reaction with the vitamin E radical, ubiquinol is able to regenerate vitamin E [23, 38]. The antioxidant function may also be related to its role in the mitochondrial electron transport chain because there is a significant release of reactive oxygen species during respiration [15, 26]. Furthermore, coenzyme Q10 is involved in extramitochondrial electron transfer in the plasma and Golgi membrane [8, 24].

Studies have shown that coenzyme Q10 supplementation decreases lipid peroxidation in plasma [38, 39, 45], improves low-density lipoprotein (LDL) resistance to in *vitro* oxidation [2, 33], and enhances the recovery of human lymphocytes from oxidative DNA damage [40], but the findings are not consistent [14, 32].

Since oxidation processes are involved in many diseases such as atherosclerosis, chronic heart failure, cancer, and Parkinson's disease, a preventive role of ubiquinol has been suggested [10, 26, 35] and could be confirmed for atherosclerotic lesions in animals if coenzyme Q10 was combined with vitamin E [39]. Moreover, favorable effects of coenzyme Q10 have been shown in chronic heart failure and hypertension [5, 36, 41]. Therefore a better supply of coenzyme Q10 might be beneficial, especially in the elderly, because ubiquinol tissue levels decrease with increasing age, possibly due to a higher requirement; e.g., following an increased production of reactive oxygen species or a reduced intake [18].

Materials and Methods

Subjects: Two hundred forty-one women aged 60 years and older were recruited by advertisement in different newspapers in the region of Hanover, Germany. Subjects with severe chronic diseases, cancer, a history of gastrointestinal resection, as well as those taking coenzyme Q10, vitamins, or enriched foods and beverages later than eight weeks before the start of intervention, were excluded. Since 21 women dropped out for different reasons, data of 220 women with a median age of 63 (range 60–91) years were included in the evaluation. All subjects gave written informed consent. The study was conducted in accordance with the Helsinki Declaration of 1964, as amended in 1996.

Intervention design: The study design was a double-blind, placebo-controlled intervention trial. Subjects were randomly assigned either to receive the capsule containing coenzyme Q10 and vitamins, or the placebo capsule, in order to take one per day with breakfast. The supplement was generously donated by Medicom Pharma AG (Springe, Germany) and contained 30 mg coenzyme Q10. In addition, the following components were included: 150 mg vitamin C, 36 mg α-tocopherol equivalents (natural vitamin E), 9 mg β-carotene, 2.4 mg thiamine, 3.2 mg riboflavin, 3.4 mg pyridoxine, 9 µg cobalamin, 400 µg folate (pteroylglutamic acid), 200 µg biotin, 34 mg niacin, 16 mg pantothenic acid, as well as 50 mg magnesium and 60 µg selenium. Both the multivitamin and the placebo capsules were soft gelatine capsules filled with soy oil. The filling of the placebo capsule was colored for identical appearance. Energy and nutrient intakes of each subject were assessed initially and at the end of the intervention by a three-day estimated food diary.

Blood parameters: Serum concentrations of coenzyme Q10, vitamins, and selenium, as well as blood lipids, were measured prior to and after six months of supplementation. Overnight fasting blood samples were taken by venipuncture and centrifuged at 4000 U/minute for 10 minutes. Serum aliquots for determination of coenzyme Q10 were stored at –20°C for four weeks and were then transported to the laboratory of the Research Society for Lung and Thoracical Diseases (FILT GmbH), Berlin. Serum aliquots for vitamin and blood lipids analysis were stored at –4°C and transported to the laboratory (Department of Clinical Chemistry of the University of Gießen) within five hours.

Ubiquinone was determined by a modified method of Podda *et al* [31] and Edlund [11]. For quantitation of ubiquinone-10, 1 mL ethanol and 10 µL coenzyme Q6 as internal standard were added to 1 mL serum. The solution was then incubated with copper sulfate for 30 minutes at room temperature in order to oxidize ubiquinol to ubiquinone. Afterwards it was centrifuged again at 2800 U/minute for 5 minutes. After precipitation of proteins, ubiquinone was isolated by n-hexane/ethanol (95/5, v/v) and measured by gradient reversed-phase high-performance liquid chromatography using a Lichrosorb RP-8 column and a mobile phase consisting of (A) acetonitrile and 2-methyl-1-propanol (85/15, v/v) and (B) water and acetonitrile (20/10, v/v). The initial conditions were 80% A and 20% B. The gradient was changed linearly over 10 minutes to 100% A at a flow-rate of 0.9 mL/min. The eluate was analyzed by ultraviolet diode array detection (RP HPLC-DAD) at a wavelength of $\lambda = 275$ nm. Coenyzme Q10 eluted with a retention time of 16.2 minutes and coenzyme Q6 with 9.3 minutes. The coenzyme Q10 content of

serum was evaluated by the peak area of ubiquinone-10 using the internal standard method (HP Chemstation Version 2.0). The correlation coefficient for the linear calibration curve for coenzyme Q10 at a concentration range of 0.12–5.78 µmol/L was 0.9975. Mean repeatability coefficient of variation was 3.3%; the detection limit was 0.116 µmol/L.

The relation of reduced and oxidized coenzyme Q10 in serum has been determined in different studies and is reported as ubiquinol/ubiquinone 95/5 [48] or 92/8 [12].

Cholesterol and triglycerides were measured enzymatically. Since coenzyme Q10 is transported with the plasma lipids, the serum concentrations depend on serum lipid levels and were significantly correlated to total plasma cholesterol ($r = 0.39$, $p = 0.000$) and to a lesser extent to triglycerides ($r = 0.19$, $p = 0.005$). After adjusting the coenzyme Q10 concentrations for cholesterol, these corrected values were no longer correlated to triglycerides ($r = 0.048$, $p = 0.483$). Therefore, all coenzyme Q10 results are shown as absolute and cholesterol-adjusted values.

Statistical analyses: Data were analyzed using SPSS 10.0. Since serum coenzyme Q10 distributions were markedly skewed, values are reported as medians and 5th through 95th percentiles. Normal distribution of all variables was tested with the Kolmogorov-Smirnov test. The statistical significance of differences between the supplemented and the placebo group was analyzed by using the two-sample t-test if data were normally distributed and the Mann-Whitney U-test if not. Comparisons for results within a group before and after supplementation were performed using paired t-tests if data were normally distributed and the Wilcoxon test if not. Correlations were analyzed by the Pearson method to identify associations among normally distributed variables and Spearman's rank correlation coefficients were calculated in the case of skewed distribution. A p value 0.05 was considered as statistically significant.

Results

The characteristics of the supplemented and control group at baseline are shown in Table I. There were no significant differences regarding age and body mass index between both groups. Fifteen women were smokers: eight of the supplemented and seven of the control group.

At baseline the median coenzyme Q10 serum concentration of all participants was 0.99 µmol/L (5–95 percentiles: 0.54–1.68 µmol/L) and ranged from 0.29 to 6.10 µmol/L. This is in the range of coenzyme Q10 levels determined in other studie [17, 48]. The laboratory reference concentration ranged from 0.92 to 1.39 µmol/L. The median cholesterol-adjusted value of the collective at baseline was 0.16 mmol/mol cholesterol (5–95 percentiles: 0.09–0.26 mmol/mol cholesterol). The median coenzyme Q10 serum concentrations of the supplemented and the control group as well as the cholesterol-adjusted values are shown in Table II. At baseline both groups did not differ in cholesterol ($p = 0.916$), triglycerides ($p = 0.701$), coenzyme Q10 ($p = 0.731$), and cholesterol-adjusted coenzyme Q10 concentration ($p = 0.365$). Adjusted coenzyme Q10 levels of the 15 smokers were not significantly different from those of nonsmokers ($p = 0.283$). There were no significant correlations between adjusted baseline values and age ($r = –0.002$, $p = 0.980$) or BMI ($r = –0.026$, $p = 0.703$). Table III shows the six-month changes for both groups.

After six months the median cholesterol-adjusted coenzyme Q10 concentration of the supplemented group was significantly increased by 106.3% (mean 117.6%; 95% CI, 102.6–132.7, $p = 0.000$) and was significantly higher than that of the control group. Cholesterol-adjusted serum concentrations of the control group increased as well by 31.3% (mean 46.2; 95% CI, 37.3-55.2, $p = 0.000$).

Table I: Baseline measurements of the study population[1]

	Supplemented group (n = 111)	Control group (n = 109)
Age (y)	63 (60–74)	64 (60–76)
Height (cm)	163 (154–174)	164 (155–174)
Weight (kg)	68.0 (52.2–88.2)	69.0 (54.5–89.5)
BMI (kg/m^2)	25.0 (20.0–33.1)	25.5 (20.4–33.0)

[1] median (5–95 percentiles)

Table II: Serum cholesterol, triglycerides and coenzyme Q10 status before and after six months of supplementation[1]

	Supplemented group (n = 111)	Control group (n = 109)
Serum cholesterol (mmol/L)		
Baseline	6.30 (4.80–7.76)	6.26 (5.00–8.13)
after Supplementation	6.13 (4.87–7.85)	6.18 (4.77–7.89)
Serum triglycerides (mmol/L)		
Baseline	1.13 (0.71–2.24)	1.13 (0.70–2.16)
after Supplementation	1.06 (0.61–2.56)	1.00 (0.59–2.32)
Serum coenzyme Q10 (µmol/L)		
Baseline	1.02 (0.54–1.81)	0.98 (0.55–1.62)
after Supplementation	1.97 (1.06–3.50)[2,3]	1.30 (0.99–2.46)[3]
Adjusted serum coenzyme Q10 (mmol/mol total cholesterol)		
Baseline	0.16 (0.09–0.27)	0.16 (0.09–0.26)
after Supplementation	0.33 (0.20–0.53)[2,3]	0.21 (0.15–0.39)[3]

[1] median (5–95 percentiles)
[2] significant differences vs. control group values: p = 0.000
[3] significant difference vs. baseline: p = 0.000

Table III: Six-month changes in cholesterol, triglycerides and coenzyme Q10 concentration[1]

	Supplemented group (n = 111)	Control group (n = 109)	p
Serum cholesterol (mmol/L)	–0.1034 (–1.50–1.07)	–0.03 (–1.37–1.01)	0.340
Serum triglycerides (mmol/L)	–0.09 (–0.64–0.72)	-0.10 (–0.69–0.58)	0.514
Serum coenzyme Q10 (µmol/L)	1.00 (0.15–2.31)	0.35 (–0.21–1.04)	0.000
Adjusted serum coenzyme Q10 (mmol/mol total cholesterol)	0.16 (0.03–0.34)	0.06 (–0.01–0.21)	0.000

[1] median (5–95 percentiles)

The extent of increase of the adjusted Q10 concentration strongly depended on the baseline concentration. In the supplemented group the six-month changes in adjusted coenzyme Q10 concentrations were inversely correlated to the baseline values (r = –0.530, p = 0.000) (Fig. 1). In the control group, however, there was no correlation between baseline values and the changes of cholesterol-adjusted coenzyme Q10 concentration (r = 0.023, p = 0.815). Furthermore, no correlation could be found between the changes of cholesterol-adjusted coenzyme Q10 concentration in the placebo group to baseline vitamin concentrations.

Since coenzyme Q10 acts as an antioxidant and is able to regenerate vitamin E [8,17], a positive correlation between both antioxidants can be assumed. At baseline the cholesterol-adjusted Q10 concentrations were significantly correlated to lipid-adjusted tocopherol levels of the complete collective (r = 0.171, p = 0.012), whereas there was a significant inverse association between adjusted plasma Q10 and beta-carotene concentration (r = –0.20, p = 0.003). This negative association is confirmed if the beta-carotene and adjusted Q10 concentrations of the control group after the intervention period were correlated (r = –0.37, p = 0.000). Since the coenzyme Q10 content of the diet was not determined, it cannot be evaluated whether the inverse relation results from different food intake patterns, because the main carotene sources are fruits and vegetables, while the main sources of coenzyme Q10 are meat, meat products, and fish [46, 47].

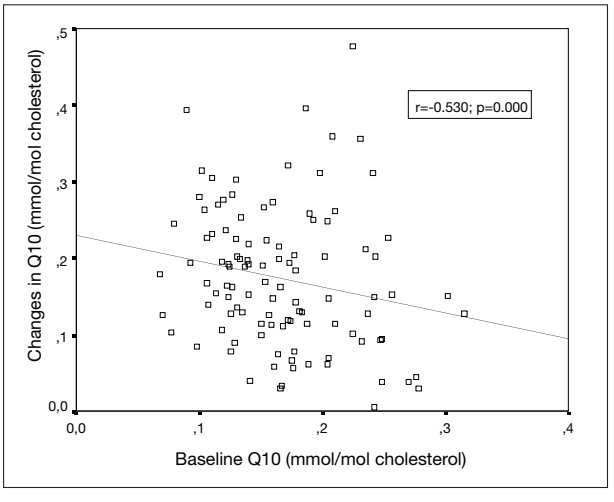

Figure 1: Correlation between changes and baseline of cholesterol-adjusted coenzyme Q10 serum concentration of the supplemented group.

No significant correlation existed at baseline in the complete collective between adjusted Q10 and plasma vitamin C (r = 0.047, p = 0.506) or plasma selenium (r = 0.057, p = 0.422), though like coenzyme Q10 selenium is also predominantly found in meat and fish.

Prior to the baseline blood sample and after six months of intervention the volunteers completed a three-day food diary (142 items). The mean daily intake of the different food groups was calculated from both food diaries. As mentioned above, the intake of coenzyme Q10 itself could not be determined since it is not included in the food data used, but we tested if the intake of the main food sources of coenzyme Q10 as well as other food groups were related to the baseline Q10 concentration. There were only weak positive associations between adjusted serum Q10 and the average daily consumption of meat and meat products (r = 0.230, p = 0.001) and alcohol (r = 0.144, p = 0.034) and an inverse association to the intake of milk and milk products (r = –0.185, p = 0.007). No association could be found between adjusted serum Q10 at baseline and consumption of fish, fat, or eggs.

Kontush *et al* [19] reported lower ubiquinol-10 serum concentrations in patients with hypertriglyceridemia or hypercholesterolemia (total plasma cholesterol > 220 mg/dL (5.69 mmol/L) or total plasma triglycerides > 200 mg/dL (2.25 mmol/L)) and indicated ubiquinol-10 concentrations adjusted for cholesterol and triglycerides. We did not differ between ubiquinol-10 and ubiquinone-10, but measured only total concentrations. Neither cholesterol-adjusted coenzyme Q10 concentrations (p = 0.111) nor cholesterol- and triglyceride-adjusted concentrations (p = 0.135) differed between the hyperlipidemic (n = 162) and the normolipidemic (n = 53) women.

Ten women took statins because of high serum cholesterol. Since HMG-CoA reductase plays an important role in the biosynthesis of coenzyme Q10, we suggested that they might have lower cholesterol-adjusted coenzyme Q10 values at baseline, but there was no significant difference between women with or without statin therapy (p = 0.157). Even if coenzyme Q10 concentrations were

adjusted for cholesterol and triglycerides there was no significant difference between both subgroups (p = 0.105).

Discussion

In our study, median Q10 concentrations of the supplemented group were increased by 106.3%, and there was an increase in the control group as well (31.3%), for which the reason is unknown. A similar increase of 40.2% without coenzyme Q10 supplementation was found in pregnant women, who received a multivitamin/mineral preparation [27]. In this case the increase might have been a result of vitamin E supplementation, which could have had a coenzyme Q10-sparing effect because both antioxidants are lipophilic. We only found a weak correlation between Q10 and vitamin E baseline levels and no association of the Q10 increase in the placebo group and baseline or final vitamin E levels. If the observed Q10 increase in the control group of 31.3% is subtracted from that in the supplemented group, the supplement effect was only an increase of 75%.

Table IV shows results from previous supplementation studies as well as our finding and indicates that a 3–6-fold increase of coenzyme Q10 dosage from 30 mg to 90 mg and to 200 mg daily results in an approximately equivalent factor of increase of plasma concentration from 75 to 522%. The different extent of increase might be a result of differences in baseline values and blood lipids as shown in our study. Moreover, different nutrient intake together with the coenzyme Q10 can influence its bioavailability since its absorption is associated with fat absorption [4]. The duration of supplementation in the range of one to six months seems to be of inferior importance.

Median baseline cholesterol-adjusted Q10 concentration of our collective was in the same range as those of a Finnish collective of mildly hypercholesterolemic subjects aged 60.7 ± 5.7 years [17]. In the Finnish study, after three-month supplementation of 200 mg (2 × 100 mg) coenzyme Q10 combined with 700 mg d-α-tocopherol daily, the plasma Q10/cholesterol ratio increased only by 221% in contrast to 522% after 200 mg coenzyme Q10 alone [17]. Though our supplement contained vitamin E as well, it is unlikely that the increase of Q10 serum levels had markedly been attenuated by vitamin E because of the lower dosages.

The results of the Finnish study indicate that ubiquinol is regenerating the tocopherol radical, since supplementation of tocopherol alone led to a reduced percentage of ubiquinol related to total Q10, which is equivalent to a deterioration of the redox status. On the other hand, coenzyme Q10 supplementation alone has been observed to increase the ubiquinol percentage of total Q10 [17].

Total plasma Q10 level in 12 hypercholesterolemic adults (16–45 years) was 1.1 ± 0.5 µmol/L [33]. The higher concentration compared to the baseline value of our collective might result from the increased cholesterol levels since the authors did not indicate the cholesterol-adjusted values [33]. In contrast to our results, in 23 young and healthy adults no correlation was found between the absolute concentration of total cholesterol and plasma ubiquinol-10 levels [29]. There was no significant correlation between the plasma concentration of ubiquinol-10 and its content in any of the lipoprotein types. As also shown by others [37], ubiquinol-10 was preferentially carried by LDL (61.54 ± 19.09%) and to a lower extent by high-density lipoprotein (HDL) (23.27 ± 13.68%) and other lipoproteins including very-low-density lipoprotein (VLDL) (15.18 ± 10.6%). Cholesterol-normalized plasma concentration of ubiquinol-10 was in the same range as that measured in LDL and HDL but significantly lower than that found in VLDL (–62%) [29]. In this study the absolute and cholesterol-adjusted plasma concentration of coenzyme Q10 were far lower than in our collective, likely due to different analytical procedures.

Table IV: Increase of coenzyme Q10 serum levels after supplementation of different coenzyme Q10 dosages

Subjects	n	Q10 (daily)	Duration	Increase Q10 serum level	Reference
Healthy elderly women	111	30 mg + multivitamin, selenium, magnesium	6 months	75%[1]	Our study
Diabetic patients, statin therapy	17	30 mg	6 months	81%	Miyake *et al,* 1999
Healthy subjects	21	90 mg	9 months	104%	Folkers *et al,* 1994
Smoking men	20	90 mg (as granulate)	2 months	168%	Priemé *et al,* 1997
Smoking men	20	90 mg (in oil)	2 months	169%	Priemé *et al,* 1997
Hyperchole-sterolemic adults	12	150 mg	1 month	354%	Raitakari *et al,* 2000
Mildly hyperchole-sterolemic, statin therapy	10	200 mg + 700 mg d-alpha-tocopherol	3 months	221%	Kaikkonen *et al,* 2000
Mildly hyperchole-sterolemic, statin therapy	10	200 mg	3 months	522%	Kaikkonen *et al,* 2000

[1] Increase in control group is subtracted, otherwise 106.3%

One-and-a-half times higher mean serum coenzyme Q10 concentrations than in our study have been found in Greenlanders from an area where the traditional Greenlandic diet predominates, with high intake of sea mammals and fish [28]. Meat and fish are main sources of coenzyme Q10, so these high levels probably reflect the diet. In contrast to our results, Q10 concentrations were positively associated with age and serum selenium in males, and according to our results, to total cholesterol in females. We did not found a correlation between the age and serum Q10 levels, likely because our collective was nearly of the same age. Although Q10 levels are thought to decrease with increasing age [18], the positive association in Greenlanders might have been a result of higher serum cholesterol concentrations in the elderly.

In coronary atherosclerosis the plasma coenzyme Q10 concentrations are not inevitably reduced. In a case-control study among male cases with coronary atherosclerosis and healthy controls, differences of absolute Q10 levels and LDL-cholesterol adjusted concentrations did not reach significance, though adjusted levels were slightly lower in cases than in controls. Absolute plasma concentrations of cases and controls (0.86 ± 0.04 and 0.83 ± 0.04 μmol/L) were lower than in our collective [42].

The effect of statin therapy on coenzyme Q10 levels is still a subject of debate, since study results are contradictory. Statins or 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) inhibitors are used widely as effective drugs in lowering serum low-density lipoprotein (LDL) concentration. Ten women of our collective were treated with different statins, and we found no difference in their cholesterol-adjusted plasma Q10 concentration compared to those without statin therapy. A randomized crossover study with pravastatin and atorvastatin also showed no effect on coenzyme Q10 levels in twelve healthy volunteers [3]. But the time of intervention in this study of only four weeks for each HMG-CoA reductase inhibitor could have been too short to reduce Q10 concentrations significantly. Older results showed a lowering effect on plasma coenzyme Q10 by HMG-CoA reductase inhibitors in healthy volunteers and hypercholesterolemic patients [16, 44].

In diabetic patients serum coenzyme Q10 levels were significantly decreased, both with (0.63 ± 0.19 μmol/L) and without (0.66 ± 0.21 μmol/L) HMG-CoA reductase inhibitor therapy compared to healthy volunteers (0.91 ± 0.26 μmol/L) [22]. Higher concentrations have been measured in diabetic patients with hypercholesterolemia (1.37 ± 0.48 μmol/L). The serum concentrations of the healthy volunteers were slightly lower than in our collective, possibly due to lower cholesterol concentrations of the young volunteers (age 32.8 ± 4.2). The authors did not report adjusted concentrations, but if the relation of mean coenzyme Q10 concentration and mean total cholesterol is considered, this assumption is confirmed. The young volunteers had a higher serum Q10/cholesterol quotient (0.19 mmol/mol total cholesterol) than our collective (median 0.16 mmol/mol total cholesterol). Oral Q10 supplementation in the diabetic patients significantly increased serum coenzyme Q10 (see Table IV) and significantly decreased cardiothoracic ratios (CTR). The CTR compares the widest heart diameter with the widest chest diameter. Normal cardiothoracic ratio is less than 1:2, a CTR of greater than 0.5 is considered as representing cardiomegaly [21]. The decrease of CTR may indicate that subclinical diabetic cardiomyopathy could be reversed by coenzyme Q10 supplementation [22]. The reported low Q10 levels in diabetic patients compared to healthy volunteers might have been a result of increased oxidative stress in diabetes because hyperglycemia depletes antioxidants and facilitates the production of free radicals. Reduced standardized plasma ubiquinol has been found in diabetics previously [20]. Studies suggest that antioxidant/oxidant balance cannot be improved by supplementation of coenzyme Q10 alone, but by combined antioxidant therapy (9, 34, 39].

Conclusion

Supplemental coenzyme Q10 is effective in raising plasma coenzyme Q10 levels. Whether the observed increase means an improvement regarding the health status of the women cannot be determined. Definite data is still missing, but there is some evidence for positive effects. Since studies have shown that coenzyme Q10 supplementation is safe up to dosages of 200 mg for 6–12 months and 10 mg for up to six years [25], additional coenzyme Q10 intake is worth considering for high-risk groups such as patients with chronic heart failure, diabetic patients, or hyperlipidemic subjects, especially those on statin therapy.

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