Determinants of plasma coenzyme Q_{10} in humans

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Abstract In the present study, we assessed the strongest determinants of plasma coenzyme Q_{10} (Q_{10}) in 518 men and women (aged 45–70 years) with a stepwise multivariate regression model. Male gender ($P < 0.001$), serum cholesterol ($P < 0.001$), serum γ-glutamyltransferase ($P < 0.001$), serum triglycerides ($P < 0.001$), age ($P = 0.017$) and 4-day alcohol consumption ($P = 0.03$) were the most important factors which were directly associated with plasma Q_{10}. The intensity of conditioning exercise ($P = 0.03$) and use of statins ($P < 0.05$) showed an inverse association with plasma Q_{10}. None of the assessed nutrients increased plasma Q_{10} levels significantly. Our results suggest that many confounding factors, in addition to serum cholesterol and triglycerides, should be taken into account when the role of plasma Q_{10} is examined in epidemiological research.

Key words: Coenzyme Q_{10}; Confounding factor; Determinant; Population study

1. Introduction

Several chromatographic measurement methods for plasma coenzyme Q_{10} (Q_{10}) have been published recently [1–3]. However, there are no previous population studies assessing either endogenous or exogenous (dietary) determinants of plasma coenzyme Q_{10} concentration in humans. This is a serious shortcoming, because measurement of plasma Q_{10} has been claimed to be of clinical significance [4–6]. Lack of this information can, however, lead to incorrect conclusions.

The range for plasma Q_{10} concentration in humans is typically 0.5–2 μmol/l [7]. It is already well established that plasma Q_{10} concentration is highly dependent on serum lipoproteins (cholesterol levels), which are the carriers of Q_{10} in the circulation [8,9]. Furthermore, there is a preliminary finding that the plasma coenzyme Q_{10} levels are higher in men than in women ($n = 10$) [10]. However, these findings have not been confirmed in population studies. In addition to endogenous factors, the diet can influence the plasma Q_{10} concentration, due to the long half-life of this coenzyme in the circulation [11]. In humans, the major dietary sources of Q_{10} are considered to be meat, fish and some vegetables [12,13].

If one is to use plasma Q_{10} levels reliably for clinical purposes, it is crucial to know which different exogenous and endogenous factors can influence their levels. The aim of this study was to identify the major determinants of plasma total Q_{10} in middle-aged and older men and postmenopausal women.

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2. Materials and methods

2.1. Study population

The present study examined 45–70-year-old smoking (>5 cigarettes/day) and non-smoking men ($n = 254$) and postmenopausal women ($n = 264$) taking part in the ASAP (Antioxidant Supplementation in Atherosclerosis Prevention) study. All subjects had a mild hypercholesterolemia, defined as serum cholesterol of at least 5.0 mmol/l at a screening visit. Twelve subjects were taking a regular HMG-CoA reductase inhibitor (statin) treatment. All subjects provided written informed consent. The study protocol was approved by the Research Ethics Committee of the University of Kuopio. Subjects were instructed to abstain from eating for 12 h and from ingesting alcohol for a week before blood sampling.

Exclusion criteria were premenopause or regular oral estrogen substitution therapy, regular intake of antioxidants, acetylsalicylic acid or any other drug with established antioxidative properties, severe obesity (body mass index > 32 kg/m^2), insulin-dependent (type 1) diabetes, uncontrolled hypertension (sitting diastolic blood pressure > 105 mm Hg) at a screening visit or any condition that would limit the mobility of the subject making study visits impossible.

2.2. Food recordings and questionnaires

The consumption of foods (including 4-day alcohol consumption) was assessed at the time of blood sampling by asking the subject to bring a 4-day food record weighed with household measures [14], which was checked by a nutritionist. The intake of nutrients was estimated using NUTRICA software based on mainly Finnish values for the nutrient composition of foods.

Intensity of conditioning activity, smoking, use of statins and mean weekly alcohol consumption (based on 12-month use) were assessed by a separate questionnaire. Weight and height for body mass index (BMI) were assessed by a nurse.

2.3. Chemical measurements

Plasma total Q_{10} levels were measured chromatographically with an electrochemical method [15]. Serum cholesterol (Kone Instruments, Espoo, Finland) and serum triglycerides (Boehringer Mannheim, Mannheim, Germany) were measured enzymatically. Serum γ-glutamyltransferase (γ-GT) activity was measured with a standardized method [16].

2.4. Statistical analysis

A number of possible determinants of plasma Q_{10} concentration, including age, physical activity, cigarette smoking, alcohol consumption, dietary intake of nutrients, medication (statins), BMI, diseases, such as history of diabetes, cancer, hypertension and atherosclerosis, biochemical factors, such as serum lipids, serum albumin (the major thiol in plasma), serum γ-GT, serum carbohydrate-deficient transferrin (CDT), hemoglobin, leukocytes and whole blood glutathione (as an endogenous antioxidant) were included in a step-up linear multivariate regression model ($P = 0.2$ for entry). Dietary antioxidants were not included in the statistical analysis because of their dependence on nutrients. In addition, variance analysis and covariance analysis (ANCOVA) were used to test differences in plasma Q_{10} levels both between men and women and between users and non-users of statins. Variance analysis was also used to test linearity across groups (P for trend).

3. Results

The means, standard deviations and ranges of determinants

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Table 1
Characteristics of the main determinants of plasma coenzyme Q_{10} ($n = 518$)

	Mean ± S.D.	Minimum	Maximum
Chemical measurements			
Plasma Q_{10} (μmol/l)	1.04 ± 0.28	0.28	2.31
Serum cholesterol (mmol/l)	6.41 ± 0.98	3.41	11.57
Serum γ-GT (U/l)	34 ± 41	1	666
Serum triglycerides (mmol/l)	1.60 ± 1.17	0.38	21.60
Anthropometric characteristics			
Gender (0 = female vs. 1 = male)	0.49 ± 0.50	0	1
Age (years)	59.9 ± 5.6	45.4	70.4
Behavioral factors			
Alcohol consumption (g/day)	3.6 ± 9.3	0.0	122.0
Mean weekly alcohol consumption (g/week)	61.6 ± 96.0	0.0	1117.4
Intensity of conditioning activity (mean METs)	5.57 ± 1.33	3.00	11.57
Use of statins (0 = non-user vs. 1 = user)	0.02 ± 0.15	0	1
Body mass index (kg/m^2)	26.1 ± 3.1	17.3	33.1
Smoking (0 = no vs. 1 = yes)	0.47 ± 0.50	0	1
Dietary nutrients			
Fish (g/day)	42.3 ± 50.2	0.0	346.6
Dairy products (g/day)	484.6 ± 270.3	15.0	1781.2
Vegetables+roots (g/day)	289.4 ± 129.5	16.3	716.9
Eggs (g/day)	24.8 ± 20.2	0.0	127.8

of plasma Q_{10} are presented in Table 1. A stepwise multivariate regression model was used to study the strongest determinants of plasma total Q_{10} concentration. Of the tested variables, serum cholesterol, serum γ-GT, male gender, serum triglycerides, 4-day alcohol consumption, age, BMI, smoking, intake of eggs and intake of vegetables+roots entered into the model and were directly (positively) associated with plasma total Q_{10} concentration (Table 2). The use of statins, the intensity of conditioning exercise, intake of fish and intake of dairy products had an inverse association. With respect to the most important determinants, serum cholesterol accounted for 20.1%, serum γ-GT for 12.0%, gender for 5.5% and serum triglycerides for 3.1% of the variation of plasma Q_{10} concentration. The variables shown in Table 2 in total accounted for 43.5% of the variation of plasma total Q_{10}. Of the biochemical measurements, hemoglobin was also entered into the model, but was not included because of its strong positive correlation with male gender. Even though self-reported alcohol consumption and serum CDT were correlated, only alcohol intake was associated with plasma Q_{10} and therefore included in the model.

Male and female subjects were also studied separately. In men ($n = 254$), the strongest directly (positively) associated determinants were serum cholesterol, serum γ-GT and serum triglycerides accounting, respectively, for 18.4%, 14.7% and 3.4% of the variation of plasma Q_{10}. In women ($n = 264$), serum cholesterol, serum triglycerides and smoking were also directly associated, accounting for 30.7%, 6.1% and 1.8% of the variation of plasma Q_{10}, respectively.

On the basis of a separate covariance analysis, there was a significant difference in plasma Q_{10} levels between genders after adjusting for all of the factors that entered into the regression model (Table 2). In men, the adjusted plasma Q_{10} levels were 13.3% higher ($P < 0.001$) than in women (1.11 ± 0.29 μmol/l vs. 0.98 ± 0.25 μmol/l, mean ± S.D.). Corresponding crude values were approximately the same as these adjusted values.

In the present study, 12 subjects were undergoing regular

Table 2
The strongest determinants of plasma total Q_{10} concentration (nmol/l) in 45–70-year-old men and postmenopausal women based on a step-up multivariate regression model

Variable	Standardized regression coefficient	Unstandardized regression coefficient	95% CI	*P*
Chemical measurements				
Serum cholesterol (mmol/l)	0.421	122.2	101.6, 142.8	< 0.0001
Serum γ-GT (U/l)	0.250	1.71	1.24, 2.18	< 0.0001
Serum triglycerides (mmol/l)	0.189	45.79	28.60, 62.97	< 0.0001
Anthropometric characteristics				
Gender (0 = female vs. 1 = male)	0.239	135.1	94.8, 175.3	< 0.0001
Age (years)	0.083	4.22	0.75, 7.68	0.017
Behavioral factors				
Alcohol consumption (g/day)	0.079	2.40	0.29, 4.51	0.026
Intensity of conditioning activity (mean METs)	−0.075	−16.1	−30.9, −1.3	0.033
Use of statins (0 = no vs. 1 = yes)	−0.068	−127.3	−252.6, −1.9	0.047
Body mass index (kg/m^2)	0.055	5.08	−1.10, 11.25	0.107
Smoking (0 = no vs. 1 = yes)	0.052	29.58	−10.96, 70.12	0.152
Dietary nutrients				
Fish (g/day)	−0.087	−0.49	−0.88, −0.11	0.012
Dairy products (g/day)	−0.077	−0.08	−0.15, −0.01	0.024
Vegetables+roots (g/day)	0.063	0.14	−0.01, 0.29	0.071
Eggs (g/day)	0.052	0.73	−0.21, 1.67	0.130

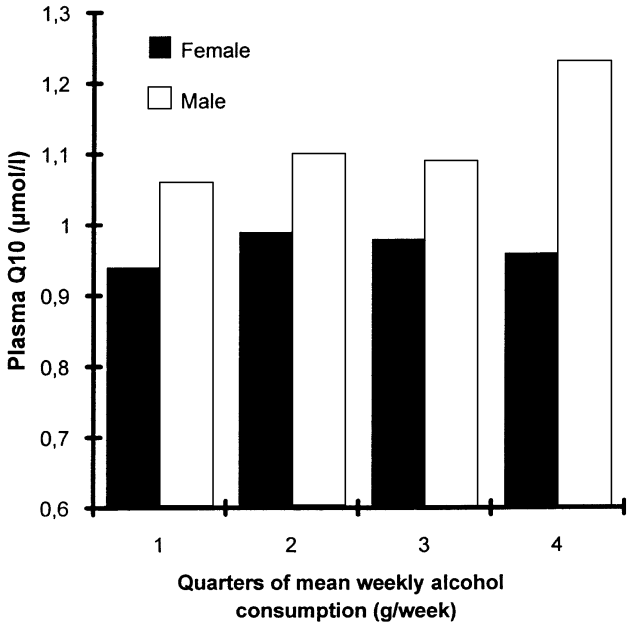

Fig. 1. Mean plasma Q_{10} levels in quarters of mean weekly alcohol consumption (g/week). In women, the cut-off values for quarters were 1.2, 9.4 and 34.2 g of alcohol per week. In men, the cut-off values were 20.8, 58.9 and 123.3 g of alcohol per week.

statin treatment. After adjusting for the strongest determinants of plasma Q_{10} (presented in Table 2), the plasma Q_{10} levels were 13.1% lower in statin users ($P = 0.047$) compared to non-users (0.86 ± 0.27 μmol/l vs. 0.99 ± 0.28 μmol/l). The corresponding crude values were 22.9% lower in statin users (0.81 ± 0.27 μmol/l vs. 1.05 ± 0.28 μmol/l).

We also assessed if there was a trend between weekly use of alcohol and crude mean plasma Q_{10} levels (in quarters) (Fig. 1). The mean weekly use of alcohol was significantly higher in men than in women (98.1 ± 121.1 vs. 26.5 ± 38.9 g/week). In men, there was also a significant positive trend across quarters ($P = 0.002$ for linearity).

Crude mean plasma Q_{10} levels are presented in Fig. 2 in four age groups (< 55, 55–59, 60–64 and 65–70 years). In women, there was a positive trend between age groups and unadjusted plasma Q_{10} values ($P = 0.016$ for linearity).

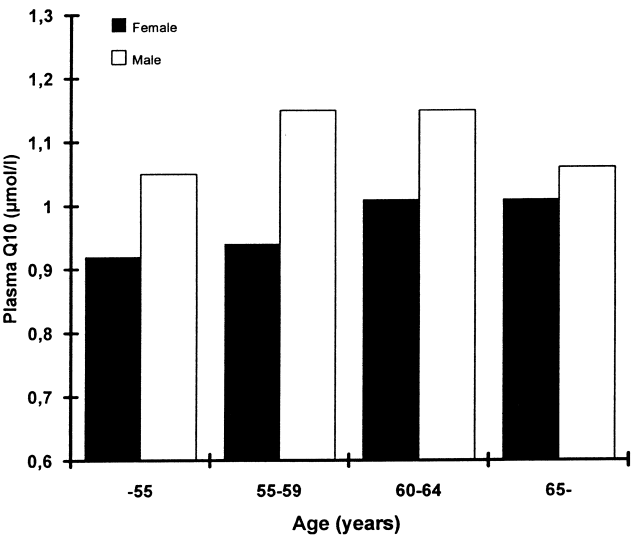

Fig. 2. Mean plasma Q_{10} levels in four age groups in men and women. Numbers of subjects were: < 55 years, 42 men and 54 women; 55–59 years, 74 men and 75 women; 60–64 years, 90 men and 80 women and 65–70 years, 48 men and 55 women.

4. Discussion

The present study is the first population study assessing both endogenous and exogenous determinants of the plasma Q_{10} concentration in humans. Some determinants of plasma Q_{10} have already been studied [8,10]. However, in previous studies, the numbers of subjects were small. The purpose of the present study was, firstly, to confirm the earlier findings at a population level and secondly, to identify new factors which could determine plasma Q_{10}. There are some previous studies suggesting that plasma Q_{10} would be of clinical significance. Low plasma Q_{10} levels have been associated with major diseases, such as coronary artery disease [4]. However, the results presented have not been sufficiently reliable due to the fact that determinants of plasma Q_{10} are only partly known.

In the present study, serum cholesterol, serum γ-GT, gender and serum triglycerides were found to be the strongest determinants of plasma Q_{10}. The association between serum cholesterol or triglycerides and plasma Q_{10} levels is understandable, since serum lipoproteins (which consist of cholesterol and triglycerides) are carriers of Q_{10} in the circulation. Furthermore, Q_{10} and cholesterol have partly a common synthesis pathway [17]. Serum γ-GT is a marker of liver damage and has been established to be a non-specific indicator of alcohol consumption. In addition to serum γ-GT, self-reported alcohol consumption was associated significantly with plasma Q_{10} levels. Liver damage, due to excess alcohol use or for any other reason, could conceivably increase plasma Q_{10} levels by releasing Q_{10} into the circulation. There is an alternative mechanism, since alcohol has been established to non-specifically stimulate metabolism in the liver, and in this way it also might accelerate the hepatic synthesis of Q_{10}. However, serum CDT, which is thought to be a specific indicator of excess alcohol use, was not associated with plasma Q_{10} levels in our study.

Many studies have shown that regular moderate alcohol consumption is associated with a decreased severity of atherosclerosis and a reduced risk of cardiovascular events [18]. Thus, low plasma Q_{10} levels in patients with severe diseases such as coronary artery disease could be attributable to lower alcohol intake among these cases than the controls.

The plasma Q_{10} concentration was significantly higher in men than in women. Adjustment for other determinants did not change this finding. It has been suggested that after 20 years of age, the total amount of Q_{10} in the human body decreases with age [19]. In the present study, age had a significant direct association with plasma Q_{10}, even after adjusting for other determinants. A similar association has also been found previously in the blood Q_{10} levels in a smaller study [20]. Furthermore, in the present study, the intensity of conditioning activity had a significant inverse association with plasma Q_{10}. There have also been previous findings indicating that exercise can decrease blood Q_{10} levels [21]. These findings suggest that plasma Q_{10} levels, at least to some degree, reflect

the need for Q_{10} of the muscles and other organs rather than their corresponding Q_{10} concentrations.

Meat and to a lesser extent fish and vegetables, such as broccoli and cauliflower, have been suggested to be the main dietary sources of Q_{10} [12,13]. In our present study, dietary factors did not significantly affect plasma Q_{10} levels, even though eggs and vegetables+roots entered into the model. Fish and dairy products had an inverse association. In men, the use of meat was significantly higher than in women. For this reason, an adjustment for gender excluded meat from the model. However, meat did not enter into the model when male and female subjects were assessed separately. Furthermore, consumption of oils did not enter into these models. These findings suggest that dietary intake of Q_{10} has only a marginal effect on plasma Q_{10} levels.

There is no agreement on the actual effects of statins on plasma Q_{10}. In many studies where statins have decreased plasma Q_{10} levels, it has often been proposed that this was due to attenuated Q_{10} synthesis [17,22]. However, in these studies, the reduction in plasma Q_{10} concentration during statin treatment could simply be a consequence of the reduction in plasma cholesterol (lipoprotein) levels [23], which are the carriers of Q_{10} in the circulation. Our present finding was that even after adjusting for the strongest determinants of plasma Q_{10}, including serum cholesterol, statin use was still associated with reduced plasma Q_{10} levels, compared to levels in non-statin users. However, though this association was significant, only 12 subjects were receiving statin treatment in the present study.

In conclusion, in addition to cholesterol and triglycerides, there are several other factors, such as gender, alcohol consumption (serum γ-GT), age, intensity of conditioning exercise, and use of statins, which should be taken into account when associations between plasma Q_{10} levels and different diseases are studied. It is possible that these factors could explain some or all of the reported associations between low plasma/serum Q_{10} levels and diseases.

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