Smoking habits and coenzyme Q10 status in healthy European adults

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Submitted: 21 July 2015
Accepted: 14 September 2015

Arch Med Sci 2016; 12, 4: 715–720
DOI: 10.5114/aoms.2016.60953

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Abstract

Introduction: Coenzyme Q10 (CoQ10) is a lipophilic endogenously synthesised antioxidant that is present in nearly all human tissues and plays an important role in mitochondrial energy production. It has been postulated that smoking has a consumptive effect on CoQ10.
Material and methods: To further define the relation between smoking and the serum CoQ10 status, 276 healthy volunteers aged 19 to 62 years were grouped into non-smokers (n = 113; 77 male, 36 female) and smokers (n = 163; 102 male, 61 female). Serum lipid profile was analysed by standard clinical chemistry. Coenzyme Q10 concentration and redox status were analysed by high-pressure liquid chromatography with electrochemical detection.
Results: Male smokers showed higher serum CoQ10 levels than female smokers. This sex-related difference was accounted for when CoQ10 was related to low-density lipoprotein (LDL) cholesterol as the main carrier of CoQ10 in the circulation. Neither LDL-adjusted CoQ10 concentration nor redox status significantly differed when smokers and non-smokers were compared. Regarding the smoking history, the number of cigarettes consumed per day did not significantly affect the CoQ10 status. Interestingly, with increasing time of smoking habit we observed increasing levels of LDL-adjusted serum CoQ10 concentration (Spearman's $p < 0.002$) and of the reduced form of CoQ10 (Spearman's $p < 0.0001$).
Conclusions: As an adaptive response to oxidative stress in long-term smokers an increased demand for antioxidant capacity may be covered by increasing levels of LDL-adjusted CoQ10 serum concentrations and by a concomitantly increased availability of the reduced, active form of CoQ10, possibly by induction of enzymes that are involved in converting CoQ10ox to CoQ10red.

Key words: cigarette smoking, coenzyme Q10, ubiquinol, oxidative stress.

Introduction

As a central electron carrier in the mitochondrial respiratory chain, coenzyme Q10 (CoQ10) is of fundamental importance in cellular bioenergetics and has gained increasing interest in research concerning conditions with altered respiratory chain activity and oxidative stress [1–3]. Oxidative stress is defined as an imbalance between pro-oxidants and anti-oxidants in favour of the former [4]. In its reduced form, CoQ10 is a potent lipophilic, endogenously synthesised antioxidant and free rad-

ical scavenger. The generation of reactive oxygen species during mitochondrial respiratory chain phosphorylation is a normal process in the life of aerobic organisms [5]. Deficiency in CoQ10 impairs mitochondrial energy output and increases production of reactive oxygen species or susceptibility towards them respectively. Inter-individual differences in CoQ10 concentration in serum and plasma have been found to be influenced by age, health and disease status, sex, ethnic origin, and nutritional factors [6–10]. Furthermore, lipid-lowering medication may result in a significant reduction in plasma CoQ10 concentrations [11]; possible associations of CoQ10 levels with statin therapy induced muscle pain [12] as well as with new onset diabetes [13] are discussed.

Free radicals can be endogenously generated, or also acquired through external sources such as cigarette smoke. Smoking is a major risk factor of morbidity and mortality, especially in cardiovascular diseases, pulmonary diseases and cancer associated with systemic inflammation and oxidative stress [14]. Free radicals present in cigarette smoke cause oxidative damage to macromolecules such as lipids, proteins and DNA. The influence of smoking habit on the CoQ10 status remains controversial. While some authors have found a positive association between smoking and the CoQ10 plasma concentration [15, 16], others found either no [10] or a negative association [17]. Also, some found that CoQ10 levels were significantly decreased in smokers, especially in females, but this gender difference was not evident in non-smokers [18].

Therefore, the present study was conducted to examine the impact of smoking on total and lipid-adjusted CoQ10 concentration and redox status in serum samples of healthy adult European blood donors. A large cohort of n = 276 subjects aged 19 to 62 years, of whom 65% were male, was considered.

Material and methods

Study population

Sample characteristics of subjects and study design have been described recently [19]. The participants in this European study collective were recruited in cooperation with the University Hospital Schleswig-Holstein (UKSH), Kiel, Germany. Out of this pool, we used 276 healthy blood donors who fulfilled the inclusion criteria based on questionnaires regarding prevalent diseases (diagnosed by a physician). Exclusion criteria for participation were diabetes, hepatic, renal or gastrointestinal diseases (chronic diarrhoea and inflammatory bowel diseases), apoplectic stroke, neurological disorders (Parkinson's disease, epilepsy, essential tremor, and restless legs syndrome), and cardiac insufficiency or coronary heart diseases. All participants denied taking medicaments regularly. They ranged in age from 19 to 62 years. A total of 65% were male. Men had a mean age of 39.4 ±10.4 years and a mean body mass index (BMI) of 26.2 ±3.9 kg/m^2, while women had mean values of 41.0 ±9.7 years and 26.4 ±5.2 kg/m^2, respectively. Subjects were grouped according to their smoking habit into non-smokers (n = 113; 77 male, 36 female) and smokers (n = 163; 102 male, 61 female). The smoking status was assessed according to the smoking history: as self-reported, the subjects smoked 1 to 60 cigarettes per day over a time course of 1 to 44 years.

The study was approved by the Ethics Committee of the Medical Faculty and was consistent with the Declaration of Helsinki. All volunteers gave written consent.

Sample preparation and analysis

Blood samples were taken after an overnight fast and immediately centrifuged. Serum samples were stored at –84°C. The simultaneous analysis of both the oxidised (ubiquinone-10) and reduced forms (ubiquinol-10) of CoQ10 was based on the method of high-pressure liquid chromatography (HPLC) with electrochemical detection as described elsewhere [20]. Briefly, as internal standards, 56 pmol of ubiquinol-9 plus 9 pmol of ubiquinone-9 (Sigma-Aldrich, Taufkirchen, Germany) in 50 µl of ethanol were added to a 50 µl serum aliquot. After hexane extraction and centrifugation (5 min, 1000 g, 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 of ethanol for injection into the HPLC system. The analytical column was a Prontosil 120-3-C18-SH PEEK column (Bischoff, Leonberg, 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.

Serum lipid profile (total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, triglycerides) was analysed by standard clinical chemistry as described elsewhere [21, 22]. Blood pressure (current systolic and diastolic value) was also measured.

Statistical analysis

Statistical analysis was performed using the Winstat software package (R. Fitch Software, Bad Krozingen, Germany). Data are expressed as the mean ± SD. To test for significant differences between two groups the Mann-Whitney U test was used. The correlation of parameters was tested by Spearman's rank correlation. The significance level was set at $p \leq 0.05$ for all tests.

Results

In the total study group (276 subjects), there was a strong positive correlation between CoQ10 and total cholesterol concentrations (Spearman's $p \leq 0.0001$, $r = +0.68$) and LDL cholesterol concentrations (Spearman's $p \leq 0.0001$, $r = +0.62$). These positive correlations were valid for men and women independently of smoking habit. HDL cholesterol level was not significantly related to CoQ10 concentration.

Table I summarizes the CoQ10 status and lipid profile in serum of subjects classified for sex and smoking habit. While total cholesterol levels did not differ, female subjects had distinctly higher HDL cholesterol and decreased LDL cholesterol and triglyceride concentrations independently of smoking habit. In conjunction with the serum lipid

Table I. Serum CoQ10 status, lipid profile and blood pressure of 276 subjects classified for gender and sex. Data are presented as mean ± SD. To test for significant differences the Mann-Whitney *U* test was used

Parameter	Gender	Non-smokers (*n* = 113)	Smokers (*n* = 163)	*P*-value
CoQ10 [µmol/l]	Male (*n* = 179)	0.877 ±0.313	1.003 ±0.372	0.03
	Female (*n* = 97)	0.780 ±0.289	0.891 ±0.325	0.08
	P ≤ (♂ vs. ♀)	0.09	0.05	
CoQ10 redox status (% oxidized in total)	Male (*n* = 179)	12.3 ±2.9	12.2 ±2.2	0.76
	Female (*n* = 97)	12.1 ±2.1	12.4 ±2.0	0.51
	P ≤ (♂ vs. ♀)	1	0.45	
Cholesterol [mmol/l]	Male (*n* = 179)	4.65 ±0.89	4.93 ±1.02	0.09
	Female (*n* = 97)	4.56 ±0.72	4.82 ±0.86	0.11
	P ≤ (♂ vs. ♀)	0.48	0.3	
Triglyceride [mg/dl]	Male (*n* = 179)	119 ±71	137 ±74	0.07
	Female (*n* = 97)	91 ±55	102 ±57	0.24
	P ≤ (♂ vs. ♀)	0.02	0.001	
HDL cholesterol [mmol/l]	Male (*n* = 179)	1.39 ±0.32	1.36 ±0.33	0.47
	Female (*n* = 97)	1.72 ±0.43	1.67 ±0.38	0.49
	P ≤ (♂ vs. ♀)	0.0001	0.0001	
LDL cholesterol [mmol/l]	Male (*n* = 179)	2.88 ±0.63	3.29 ±0.97	0.16
	Female (*n* = 97)	2.77 ±0.72	3.06 ±0.90	0.18
	P ≤ (♂ vs. ♀)	0.09	0.01	
CoQ10/cholesterol [µmol/mol]	Male (*n* = 179)	188 ±56	201 ±50	0.07
	Female (*n* = 97)	170 ±59	183 ±49	0.10
	P ≤ (♂ vs. ♀)	0.06	0.03	
CoQ10/LDL cholesterol [µmol/mol]	Male (*n* = 179)	294 ±94	309 ±84	0.11
	Female (*n* = 97)	290 ±106	313 ±107	0.22
	P ≤ (♂ vs. ♀)	0.73	0.79	
Blood pressure systolic [mm Hg]	Male (*n* = 179)	133 ±14	134 ±16	0.48
	Female (*n* = 97)	124 ±12	124 ±15	0.87
	P ≤ (♂ vs. ♀)	0.002	0.0001	
Blood pressure diastolic [mm Hg]	Male (*n* = 179)	79 ±9	80 ±9	0.29
	Female (*n* = 97)	76 ±8	76 ±8	0.79
	P ≤ (♂ vs. ♀)	0.09	0.01	

profile, male smokers had higher total CoQ10 and cholesterol-adjusted CoQ10 concentrations; however, when related to LDL cholesterol, the sex-related differences in CoQ10 levels was accounted for.

The comparison of the CoQ10 status and lipid profile of smokers versus non-smokers revealed no significant differences. Male smokers showed slightly higher total CoQ10 concentrations, a difference which was accounted for when CoQ10 concentration was related to LDL cholesterol levels. Furthermore, smokers and non-smokers showed no significant differences regarding blood pressure. However, men in comparison to women had distinctly higher systolic and slightly higher diastolic blood pressure.

Within the group of smokers (n = 163) the smoking history definitely influenced blood pressure. There was a positive correlation between the number of cigarettes consumed per day and systolic (Spearman's $p \leq 0.0002$, $r = +0.29$) as well as diastolic blood pressure (Spearman's $p \leq 0.02$, $r = +0.18$). Furthermore, the smoking duration in years showed positive correlations with systolic (Spearman's $p \leq 0.001$, $r = +0.26$) and diastolic blood pressure (Spearman's $p \leq 0.0002$, $r = +0.29$). Whereas the number of cigarettes had no effect on CoQ10 status, there was a positive correlation with the duration of smoking and lipid-adjusted CoQ10 concentrations (Figure 1 A). Smoking had no influence on the proportion of the oxidized or reduced forms within total CoQ10; however, with increasing total concentrations the absolute concentration of ubiquinol (reduced form) significantly increased in long-term smokers (Figure 1 B).

Discussion

Virtually all CoQ10 in circulation is associated with lipoproteins, the main proportion being carried by LDL cholesterol [23]. CoQ10 is considered the main antioxidant in LDLs. This explains the anticipated positive correlation of CoQ10 concentrations with total cholesterol and LDL cholesterol levels. In the present study, these associations were valid for men and women independently of smoking habit. Al-Bazi *et al.* [18] found a significant positive correlation of CoQ10 plasma concentrations with total cholesterol and LDL cholesterol only in female smokers.

As shown by the present findings, male smokers showed higher total serum CoQ10 levels than female smokers. The sex-related difference was accounted for when CoQ10 concentration was related to LDL cholesterol. This stresses the necessity to relate CoQ10 concentrations in the blood to lipid concentrations, preferably to LDL cholesterol concentrations as the main carrier of CoQ10 in the blood [23]. These findings were confirmed by a study of Miles *et al.* [10], who showed that significantly higher total CoQ10 concentrations in self-reported healthy men in comparison to women were accounted for when related to LDL cholesterol. This working group also confirmed that the CoQ10 levels of non-smoker versus cigarette-smokers did not differ. In contrast, Al-Bazi *et al.* [18] found that CoQ10 concentrations were significantly lower in smokers, especially in females, even when adjusted for LDL cholesterol. Kontush *et al.* [17] reported that the proportion of reduced CoQ10 (ubiquinol) was significantly lower in smokers versus non-smokers, even when normalized to plasma lipids; however, they found no sex-related differences.

In the present study, the concentration of blood lipids did not differ significantly between smokers and non-smokers, as confirmed by others [24]. Interestingly, there are findings on the influence of tobacco smoking on LDL subfraction profile which indicate that smoking is associated with a decrease in the proportion of small, dense LDL particles [24, 25]. The densest LDL subfraction

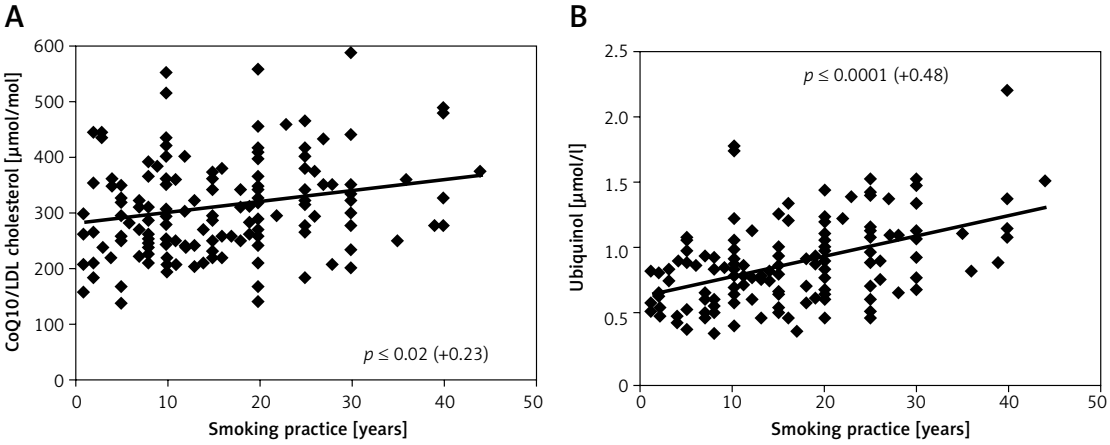

Figure 1. Correlation of LDL-adjusted serum CoQ10 (**A**) and ubiquinol (reduced CoQ10) concentration (**B**) versus duration of smoking habit in 163 smokers. The correlation of parameters was tested by Spearman's rank correlation (correlation coefficient in brackets)

was found to contain the lowest CoQ10 levels associated with increased susceptibility to oxidation when compared to the lighter counterparts [26]. In the present study, we regrettably gained no information on the LDL subfraction profile; however, smoking did not influence the CoQ10 redox status in serum overall.

It has been shown that blood pressure – as verified in the present study – and heart rate increase during smoking and that these effects are specifically associated with nicotine [27]. Generally, an "unhealthier" life style in smokers may be anticipated. Smokers have been found to eat less fruit and vegetables than non-smokers, leading to lower vitamin E, vitamin C, and carotene intake [28]. Cigarette smoke contains superoxide and other reactive oxygen species (ROS) which may enhance oxidative stress [29]. Smoking may weaken the antioxidative defence system [28, 30–33], even in passive smokers [34]. Smoking of a single cigarette was shown to temporarily decrease the concentration of serum antioxidants such as ascorbic acid [35]. The redox status of CoQ10 has been suggested to be a useful biomarker of oxidative stress [36]. In its reduced form CoQ10 is one of the most potent endogenously synthesized lipophilic antioxidants [37]. A shift towards oxidized CoQ10 is likely a sign of increased oxidative stress [17, 38, 39], whereas a shift towards reduced CoQ10 may be regarded as an endogenous compensatory response towards an increased demand of antioxidant capacity [40]. In smokers increased oxidative stress and increased demand for antioxidative capacity may be reflected in a shift in the redox status of CoQ10 as a potential biomarker for oxidative stress. However, the present findings revealed no differences regarding the CoQ10 redox status of smokers versus non-smokers. Interestingly, within the group of smokers there was a positive correlation between the number of years of smoking and LDL-adjusted CoQ10 concentrations, presumably an adaptive response to oxidative stress, since higher levels of CoQ10 in lipoproteins have been directly related to higher resistance to initiation of lipid peroxidation [41, 42]. However, future studies should provide additional information on the underlying cellular and molecular mechanisms by which smoking may affect CoQ10 status.

In conclusion, with increasing duration of the smoking habit the demand for antioxidant lipoprotein protection may be covered by increasing levels of LDL-adjusted CoQ10 concentrations accompanied by increased availability of the reduced, active form of CoQ10 in long-term smokers. This shift in redox capacity may be regarded as an adaptive response to oxidative stress induced by smoking. Thus, smoking may induce those enzymes that are involved in converting CoQ10ox to CoQ10red. Nevertheless, this response induced by smoking should not be interpreted as beneficial, because smoking per se causes a wide range of harmful effects, and the described changes in the CoQ10 status might not be sufficient to compensate for the adverse risk factors.

Acknowledgments

This work was supported by the patients' self-help group "Elterninitiative Tumorkranker Kinder e.V. der Vestischen Kinderklinik Datteln", Germany, and by the foundation "Peter und Ruth Wirts Stiftung", Switzerland. We thank all participants of the study cohort for their invaluable contribution to the study. The popgen 2.0 network is supported by a grant from the German Ministry for Education and Research (01EY1103). Determining and analysing the coenzyme Q10 status in the large study population was supported by Kaneka Corporation, Japan.

Conflict of interest

The authors declare no conflict of interest.

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