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Coenzyme Q10: Absorption, Antioxidative Properties, Determinants, and Plasma Levels

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The purpose of this article is to summarise our studies, in which the main determinants and absorption of plasma coenzyme Q10 (Q10, ubiquinone) have been assessed, and the effects of moderate dose oral Q10 supplementation on plasma antioxidative capacity, lipoprotein oxidation resistance and on plasma lipid peroxidation investigated. All the supplementation trials carried out have been blinded and placebo-controlled clinical studies.

Of the determinants of Q10, serum cholesterol, serum triglycerides, male gender, alcohol consumption and age were found to be associated positively with plasma Q10 concentration. A single dose of 30 mg of Q10, which is the maximum daily dose recommended by Q10 producers, had only a marginal elevating effect on plasma Q10 levels in non-Q10-deficient subjects. Following supplementation, a dose-dependent increase in plasma Q10 levels was observed up to a daily dose of 200 mg, which resulted in a 6.1-fold increase in plasma Q10 levels. However, simultaneous supplementation with vitamin E resulted in lower plasma Q10 levels. Of the lipid peroxidation measurements, Q10 supplementation did not increase LDL TRAP, plasma TRAP, VLDL+LDL oxidation resistance nor did it decrease LDL oxidation susceptibility *ex vivo.* Q10 with minor vitamin E dose neither decreased exercise-induced lipid peroxidation *ex vivo* nor muscular damage. Q10 supplementation might, however, decrease plasma lipid peroxidation *in vivo*, as assessed by the increased proportion of plasma ubiquinol (reduced form, $Q10H_2$) of total Q10. High dose vitamin E supplementation decreased this proportion, which suggests *in vivo* regeneration of tocopheryl radicals by ubiquinol.

Keywords: α-Tocopherol; Coenzyme Q10; Determinants; Lipid peroxidation; Oxidation resistance; Plasma levels

INTRODUCTION

There is accumulating evidence to suggest that lipid peroxidation (oxidation of cholesterol and polyunsaturated fatty acids) plays an important role in the progression of severe diseases, such as atherosclerosis.[1–3] Even though the coenzyme Q10 (Q10) concentration is very low in plasma, compared with other antioxidants or other organs,[4–6] there are several uncontrolled *in vitro* and *ex vivo* studies suggesting that Q10 is an effective lipid soluble antioxidant increasing oxidation resistance, tested in different model systems including biological membranes, plasma lipoproteins and lymphocytes.[7–13] However, there are only a few small uncontrolled clinical studies[12,14] concerning the antioxidative efficiency of orally supplemented Q10 in human plasma.

Strenuous exercise has been suggested to increase oxidative stress and to decrease oxidation resistance in the human body.[15] The effect of Q10 supplementation on exercise-induced muscle damage and oxidative stress has been investigated in rats and in humans, but the existing data are sparse and inconsistent.[16–18] Furthermore, in previous studies, the amount of subjects and the scale of performed measurements have been minute.

The antioxidative efficiency of orally supplemented vitamin E has been shown in isolated lipoproteins exposed to high radical flux *in*

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vitro.[19–22] There is a growing body of evidence indicating that during low radical flux conditions *in vitro*, supplemented α-tocopherol (vitamin E) can accelerate rather than inhibit the lipid peroxidation of isolated lipoproteins.[23,24] The role of co-antioxidants is not clear in this antioxidative/prooxidative function of vitamin E. Besides vitamin C,[25] Q10 may also recycle tocopherols, although the evidence for this comes from *in vitro* studies.[26] However, the regenerative efficacy of Q10 is highly dependent on the reduction rate of oxidised Q10. At tissue level, several enzymes have been found to have activity to regenerate Q10. The role of cytosolic two-electron quinone reductase, DT-diaphorase, as a regenerator of ubiquinone, is now well established.[27] There may also be other enzymes responsible for the reduction of Q10 in the cells.[28,29] In plasma, the reduction mechanism for Q10 is unclear. However, the proportion of plasma ubiquinol (reduced Q10, $Q10H_2$) of total Q10 has been shown to be decreased in major diseases, such as coronary artery disease and hyperlipidemia,[30,31] suggesting that the regeneration of Q10 is ineffective during the conditions of increased oxidative stress, and that the measurement of this ratio could be of clinical significance.

There have been no controlled clinical studies testing the effects of moderate oral Q10 supplementation on plasma antioxidative capacity, lipid peroxidation and lipoprotein oxidation resistance in humans. In addition, there has been no *in vivo* evidence of the interaction between plasma Q10 and vitamin E, and little information of the effect of these antioxidants on the proportion of plasma $Q10H_2$ of total Q10. Therefore, we evaluated the antioxidative efficacy of supplemented Q10 in several blinded, randomised and controlled clinical supplementation studies. In addition, we studied pharmacokinetics, plasma levels and major determinants of plasma Q10 in humans.

MATERIALS AND METHODS

In our studies,[32–35] the main exclusion criteria were: regular intake of any drug with antioxidative properties, severe obesity, insulin dependent (type 1) diabetes, malabsorption and other severe diseases leading to difficulties in the participation in the study. All the study protocols were approved by the Research Ethics Committee of the University of Kuopio, and all the subjects provided a written informed consent.

The main determinants of plasma Q10 were assessed in the subjects of ASAP (Antioxidant Supplementation in Atherosclerosis Prevention) study.[36] The ASAP is a factorial double-masked placebo-controlled randomised clinical trial concerning the effect of a 3-year vitamin E and/or vitamin C supplementation in the prevention of atherosclerosis progression in smoking and non-smoking 45–69 year old men and postmenopausal women ($n = 520$). On the basis of completely filled food recordings available, a sub-set of 518 men and women taking part in the baseline visit were included in the Q10 study.[32]

The effect of a 2-month oral Q10 supplementation on the oxidation resistance and antioxidative capacity of combined very-low-density and low-density lipoprotein (VLDL+LDL) fraction were studied in 60 smoking men (23 ± 9 cigarettes per day, age 46 ± 7 years, mean ± SD). They were randomised into three groups to receive oil-based or granular Q10 (90 mg per day) or placebo for 2 months. In addition, a 12 h pharmacokinetic study (five subjects per group) was performed with the first and the last doses.[33]

To study whether exercise-induced oxidative stress or muscular damage can be decreased by oral Q10 and low dose vitamin E supplementation, 37 moderately trained male marathon runners were randomly allocated to receive either 90 mg of oil-based Q10 and 13.5 mg of D-α-tocopheryl acetate daily (18 men) or placebo (19 men) for 3 weeks before a marathon (42 km) run.[34] In addition, we investigated both the effect of antioxidant supplementation and exercise on the proportion of plasma $Q10H_2$ of total Q10, used as an indication of plasma redox status *in vivo*. Exercise-based dehydration was taken into account by haematocrit and haemoglobin corrections.

To test interaction between Q10 and vitamin E in plasma levels and in antioxidative efficacy, we conducted a double-masked, double-blind clinical trial in 40 subjects with a mild hypercholesterolemia and statin treatment.[35] Subjects were randomly allocated to parallel groups to receive either oil-based Q10 (200 mg daily), D-α-tocopherol (700 mg daily), both antioxidants or placebo for 3 months. To assess the effects of vitamin E and Q10 supplementation on lipid peroxidation and antioxidative capacity of human plasma, we measured, besides the oxidation resistance of LDL *ex vivo*, the proportion of plasma $Q10H_2$ of total Q10, the plasma ascorbate/total ascorbic acid ratio and the plasma ascorbyl radical concentration.

More detailed descriptions of different measurement methods have been presented in the original articles published previously.[32–36] In brief, the most important measurements, plasma total Q10 and the proportion of $Q10H_2$ of total Q10 were measured by an HPLC with electrochemical detection.[37] Plasma vitamin E, vitamin C, malondialdehyde and LDL-(proportion of electronegatively charged LDL to total LDL) were measured by chromatographic methods with UV/Vis detection. Lipoprotein oxidation

susceptibility was measured by either copper or hydrogen peroxide + hemin-based induction of oxidation. In copper induction, accumulation of conjugated dienes was measured photometrically at 234 nm. In hydrogen peroxide + hemin-induced oxidation, degradation of the hemin rings was followed photometrically at 405 nm. Antioxidative capacity of plasma and LDL (plasma TRAP and LDL TRAP) were measured by using ABAP (2,2′-azobis(2-amidinopropane) dihydrochloride) and AMVN (2,2′-azobis(2,4-dimethylvaleronitrile)) as inducers of oxidation, and the luminol-enhanced chemiluminescence was used to follow peroxyl radical reactions. Plasma ascorbyl radical concentration was measured by electron spin resonance spectroscopy (ESR). Serum cholesterol and triglycerides were determined with enzymatic colorimetric tests with an autoanalyser. Serum gamma-glutamyltransferase (γ-GT) activity was measured with a standardised method. The consumption of foods (including alcohol consumption) was assessed by a 4-day food recording following NUTRICA software based on mainly Finnish values for the nutrient composition of foods. Other behavioural factors were assessed based on a separate questionnaire.

In the statistical analyses, a step-up linear multivariate regression model (p 0.2 for entry) was used to study determinants of plasma Q10. In the supplementation studies, one-way analysis of variance (ANOVA), and covariance (MANOVA), and t-tests were used in addition to non-parametrical tests to analyse differences and changes between and within the treatment groups. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Absorption and Plasma Levels of Q10

Following supplementation, there was some individual variation in the increase of plasma Q10 levels between subjects. Table I summarises the mean effects of oral Q10 supplementation on plasma Q10 levels in our trials.

On the basis of our studies ($n = 705$), we also determined reference intervals (mean ± 2 SD) for plasma total Q10. In men, the reference interval was 0.40–1.72 μmol/l, and in women, 0.43–1.47 μmol/l. The distributions of plasma Q10 levels are presented in Fig. 1. Both statin users and non-users were included in the distributions. Exclusion of statin users, 15 men and 37 women, did not change the reference intervals determined.

Two-month Supplementation Study in Smoking Men

Oil-based capsule elevated Q10 in plasma by 178% and in VLDL+LDL by 160%. The granular preparation increased Q10 in plasma by 168% and in VLDL+LDL by 127%. However, the 2-month Q10 supplementation did not increase the oxidation resistance of VLDL+LDL fraction, as assessed by copper or hemin+H_2O_2 induced VLDL+LDL oxidation and total antioxidative capacity of LDL. Neither of the supplementations decreased plasma malondialdehyde concentration (Table II). The first and the last doses were used to carry out a 12 h pharmacokinetic study (five subjects per group), which indicated that a single dose of 30 mg had only a marginal effect on the plasma levels of Q10.

Marathon Study

A 3-week supplementation with 90 mg of oil-based Q10 and 13.5 mg of D-α-tocopherol acetate daily resulted in that, just before the run, plasma Q10 was 282% and plasma vitamin E was 16% higher in the supplemented group, than in the placebo group. Also the proportion of plasma ubiquinol of total Q10, an indication of plasma redox status *in vivo*, was significantly higher in the supplemented group, compared to the placebo group ($p < 0.001$ for difference). The exercise-induced lipid peroxidation was significantly raised in both study groups, as assessed by the elevated proportion of electronegatively charged LDL (LDL^-) of LDL ($p < 0.001$ for change) and the increased susceptibility of lipoproteins to copper induced oxidation ($p < 0.001$ for change). However, the supplementation had no effect on lipid peroxidation or on muscular damage (increase in serum creatine kinase activity or in

TABLE I Mean increase in plasma Q10 levels following varying dose oral supplementation with oil or granule-based Q10

Q10 capsule	Daily dose	Duration of supplementation	Fold increase in plasma Q10
Oil	30 mg ($n = 5$)	Single dose	Marginal
	90 mg ($n = 10$)	2 days	2.5
	90 mg ($n = 10$)	7 days	3.3
	90 mg ($n = 20$)	2 months	2.8
	200 mg ($n = 10$)	3 months	6.5
	200+700 mg of D-α-tocopherol ($n = 10$)	3 months	3.2
Granule	30 mg ($n = 5$)	Single dose	Marginal
	90 mg ($n = 20$)	2 months	2.7

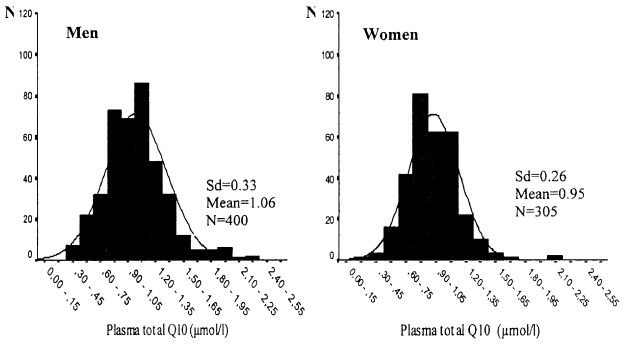

FIGURE 1 Summary of the distribution of plasma total Q10 concentration in the subjects who participated in our studies ($n = 705$). The values presented are baseline values (not supplemented values). Men are 25.1–70.1 years old (mean 54.5 years) and women 22.1–70.3 years old (mean 58.7 years). *N*=number of subjects.

plasma lactate levels), induced by exhaustive exercise. Plasma ascorbate, Q10, whole blood glutathione and serum uric acid concentrations increased during the exercise, elevating significantly the TRAP value of plasma by 10.3% ($p < 0.001$ for change) and the proportion of plasma $Q10H_2$ of total Q10 by 4.9% ($p < 0.001$ for change).

Three-month Study in Statin Users With Elevated Serum Cholesterol

A three-month supplementation with 200 mg of oil-based Q10 daily increased plasma total Q10 by 551% and daily dose of 700 mg of D-α-tocopherol plasma vitamin E by 144%. In the group that received both antioxidants, the increase of plasma Q10 was 223% and that of plasma vitamin E 129%. Thus, in the group that received both antioxidants, the increase in plasma Q10 levels was attenuated significantly, compared to the Q10 group ($p < 0.001$). Only vitamin E supplementation increased significantly the oxidation resistance of isolated LDL *ex vivo* ($p < 0.0001$ for the difference in change of overall oxidation susceptibility), compared to the placebo group. Simultaneous Q10 supplementation did not increase this antioxidative effect of vitamin E. Q10 supplementation increased and vitamin E decreased significantly the proportion of ubiquinol of total Q10, compared to the placebo group. Though vitamin E could decrease ubiquinol, it had no effect on the oxidation rate of plasma vitamin C (assessed as ascorbate or ascorbyl radical concentration or as the ascorbate/total ascorbic acid ratio).

Determinants of Plasma Total Q10

Of the determinants of plasma Q10, serum cholesterol ($r = 0.421$, $p < 0.0001$), serum γ-GT ($r = 0.250$, $p < 0.0001$), male gender ($r = 0.239$, $p < 0.0001$), serum triglycerides ($r = 0.189$, $p < 0.0001$), age ($r = 0.083$, 4-day alcohol consumption ($r = 0.079$, $p = 0.026$), intake of vegetables+roots ($r = 0.063$,

TABLE II Effect of Q10 and vitamin E dose supplementation on different indicators of lipid peroxidation *in vivo* or *in vitro*

Study and daily dose	Plasma $Q10H_2$/ tot. Q10 ratio	LDL or plasma TRAP	Cu^{2+}-induced VLDL + LDL/LDL oxidation	Hemin + H_2O_2-induced LDL oxidation	Plasma malondialdehyde
In smoking men ($n = 60$)					
(1) Oil/granule-based Q10 (90 mg)	N.D.	↑	↑	↑	↑
In marathon runners ($n = 37$)					
(1) Oil-based Q10 (90 mg) combined with a small D-α-tocopherol dose (13.5 mg)	↑	↑	↑	N.D.	N.D.
In statin users with elevated serum cholesterol ($n = 40$)					
(1) Oil-based Q10 (200 mg)	↑	N.D.	↑	N.D.	N.D.
(2) D-α-tocopherol (700 mg)	↓	N.D.	→	N.D.	N.D.
(3) Both (200+700 mg)	↑	N.D.	↓	N.D.	N.D.

In addition, none of the supplements had effect on plasma ascorbate or ascorbyl radical concentration or on the ascorbate/total ascorbic acid ratio. →, no effect; N.D., was not measured.

$p = 0.071$), body mass index ($r = 0.055$, $p = 0.017$), smoking ($r = 0.052$, $p = 0.152$) and intake of chicken eggs ($r = 0.052$, $p = 0.130$) were directly (positively) associated with plasma total Q10 concentration. Intake of fish ($r = -0.087$, $p = 0.012$), intake of dairy product, ($r = -0.077$, $p = 0.024$), the intensity of conditioning activity ($r = -0.075$, $p = 0.033$) and the use of statins ($r = -0.068$, $p = 0.047$) 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 present in the plasma Q10 concentration. The plasma Q10 levels, adjusted for the variables described above, were 13.3% higher ($p < 0.001$) in men than in women (1.11 ± 0.29 vs. 0.98 ± 0.25 μmol/l, mean ± SD) and 13.1% lower in statin users ($p = 0.047$), compared to non-users (0.86 ± 0.27 vs. 0.99 ± 0.28 μmol/l).

DISCUSSION

Our results suggest that supplemented Q10 is not an important antioxidant on the basis of measurements at high radical flux conditions *in vitro*, whereas it might act as an *in vivo* antioxidant, either directly or by vitamin E regeneration. A summary of the results of different lipid peroxidation measurements is shown in Table II.

There is cumulative evidence suggesting that the antioxidative/pro-oxidative function of a molecule could be dependent on the strength of the radical flux used under the test conditions. For example, the antioxidative efficiency of orally supplemented vitamin E has been shown in isolated lipoproteins exposed to high radical flux *in vitro*.[19–22] On the other hand, there are findings which indicate that during low radial flux *in vitro*, supplemented α-tocopherol could accelerate rather than inhibit the lipid peroxidation of isolated lipoproteins.[23,24] In this article, the border between low and high radical flux conditions has been defined as a strength of radical flux at which α-tocopherol switches from being a pro-oxidant to acting as an antioxidant. According to *in vitro* experiments, this cut-off point is achieved in a mixture containing 0.6 μmol/l of copper per 100 mg of lipoprotein/l.[38] Correspondingly, an AAPH concentration of ≤4 mmol/l per 100 mg of lipoprotein/l results in a low radical flux conditions.[38,39] Furthermore, it has been suggested in this article that there is a low radical flux in the circulation. On the basis of these points, we have discussed in this article of the antioxidative function of plasma Q10 and vitamin E.

Q10 At High Radical Flux Conditions

Our randomised and placebo-controlled clinical supplementation studies suggest that Q10 is not an effective antioxidant at high radical flux conditions *ex vivo*.[33–35] In sedentary smokers or in moderately trained healthy athletes during an exhaustive exercise, a daily oral Q10 supplementation of 90 mg, did not increase the oxidation resistance of VLDL+LDL (3.30 μmol of copper per 100 mg of lipoprotein), the antioxidative capacity of LDL (8 mmol of AMVN per 100 mg of lipoprotein, approximation) or plasma (70 mmol of AAPH per 100 mg of lipoprotein, approximation), or decrease the exercise-induced muscular damage. Furthermore, a high dose of 200 mg of Q10 daily did not elevate the oxidation resistance of LDL ((3.30 μmol/l of copper per 100 mg lipoprotein/l) nor did it increase the antioxidative efficacy of vitamin E in slightly hypercholesterolemic subjects. In our studies, the copper to lipoprotein and the AMVN to lipoprotein ratios (radical flux condition) have been rather similar to the previous cross-sectional high radical flux studies where a positive response was obtained.[10,11]

A shortcoming of Q10 at high radical flux conditions is that its plasma concentration is very small even after supplementation. Furthermore, it seems that there is no regeneration mechanism for oxidised Q10, either in plasma *ex vivo*, or in isolated lipoproteins.[40] This causes a decrease in the proportion of ubiquinol of total Q10 during the sample preparation, attenuating the already small ubiquinol pool of lipoproteins. We have found that the proportion of ubiquinol of total Q10 decreases from 84% in the fresh EDTA plasma to 74% in LDL (after 2.5-h ultracentrifugation) and to 57% in the VLDL+LDL fraction (after 23-h ultracentrifugation).[37] Thus, it is likely that the remaining ubiquinol pool is consumed very rapidly during high radical flux conditions without affecting the lag time of diene accumulation or the TRAP value.

Finally, the present results support the findings of previous supplementation[41] and cross-sectional studies that firstly, Q10 is not an important plasma antioxidant at high radical flux conditions[39] and secondly, Q10 contributes only 0.1–0.4% of the plasma total antioxidative capacity.[42] The contribution of Q10 to LDL TRAP has been proposed to be around 2.5%.[43]

Q10 At Low Radical Flux Conditions

Under low radical flux conditions, the proportion of plasma ubiquinol of total Q10 has been suggested to be an indicator of plasma lipid peroxidation *in vivo*.[30,31] In our studies,[34,35] supplementation with Q10 increased this proportion. We suggest that this was due to attenuated oxidative stress or increased antioxidative capacity *in vivo*. The mechanism for this antioxidative function of Q10 could be vitamin E regeneration. Vitamin E supplementation with a

daily dose of 200 mg decreased significantly the proportion of plasma ubiquinol of total Q10,[35] which suggests that ubiquinol was consumed for vitamin E regeneration. The supplementation did not affect the plasma ascorbate or ascorbate radical concentration or the ascorbate/total ascorbic acid ratio. This result suggests that, at high Q10 levels, supplemented vitamin E consumes ubiquinol rather than vitamin C. It is also possible that plasma vitamin C radicals and dehydroascorbate molecules are recycled very effectively, which could explain why no increase in their levels was observed. Alternatively, the decrease in the proportion of $Q10H_2$ of total Q10 might be due to a possible pro-oxidative effect of supplemented α-tocopherol at low radical flux conditions *in vivo*.[23,24] Exhaustive exercise increased the proportional amount of ubiquinol in plasma during the marathon run. Thus, the increase in the Q10 ratio may indicate that, in addition to an attenuated lipid peroxidation, there was an increased plasma antioxidative capacity, or both.

Previously, in low radical flux studies, the consumption of ubiquinol has been monitored in isolated lipoproteins. These studies also give the most convincing evidence concerning antioxidative efficacy of Q10. At low radical flux conditions, accumulation of lipid hydroperoxides has been found only after total consumption of LDL ubiquinol, while the other antioxidants, including vitamin E, have not yet been consumed.[12] Under these conditions, ubiquinol has also prevented the tocopherol-mediated accumulation of lipid hydroperoxides.[26]

We also measured an end-product of lipid peroxidation, plasma malondialdehyde.[33] This measurement did not indicate that supplemented Q10 would have antioxidative capabilities in plasma in smoking men. This result is in disagreement with a small uncontrolled study, in which 90 mg of Q10 daily for 2 weeks lowered plasma TBARS concentration.[14] However, we have to remember that these assays rarely measure the TBARS content of the sample *in vivo*, because a part of the MDA or TBARS measured are formed during the sample heating stage.[44,45] Furthermore, Q10 supplementation did not spare other plasma antioxidants *in vivo*, i.e. there was no secondary effect in its antioxidative function.

Absorption of Q10 Preparations

The increase in plasma Q10 levels following supplementation was similar to that in previous studies.[46–49] However, differences in the Q10 preparations, subjects and doses complicates the comparison of results between different studies. Previous studies have suggested that oil-based preparations would be best absorbed.[46,48] We observed no difference in the absorption between the oil and granule-based preparations. A single dose of 30 mg, which is the maximum daily dose recommended by Q10 producers, had only a marginal elevating effect on plasma Q10 levels.[33] Following supplementation, a dose-dependent increase in plasma Q10 levels was observed up to a daily dose of 200 mg, which resulted in a 6.1-fold increase in plasma Q10 levels. In some subjects, already a 2-day supplementation with 90 mg, increased the plasma Q10 levels to its dose-dependent maximum.[33,35]

However, the simultaneous vitamin E supplementation decreased the increase of plasma Q10 levels by more than fifty percent.[35] This is a new finding and therefore worth further investigation. There may be competitive absorption between Q10 and vitamin E in the gut. Another possibility is that the plasma concentrations are regulated at the lipoprotein level. It has been suggested that both lipoprotein levels and the forms of vitamin E are regulated by tocopherol binding protein in the liver.[50] This protein might also regulate the transport of orally supplemented Q10 into lipoproteins, leading to selective distribution between these two vitamins. Furthermore, the redox status of these antioxidants can possibly affect their absorption in the gut. The cholesterol (+ triglyceride)-corrected plasma levels were also calculated, but this correction did not affect the initial results.

The discovery of preparations containing solubilised Q10[51] has increased the absorption and bioavailability of Q10, compared to older preparations. Antioxidative efficacy of these new commercial products should be tested in future clinical trials.

Determinants of Plasma Q10

It was confirmed at a population level that in addition to high serum cholesterol and triglycerides, high alcohol intake and male gender were associated with elevated plasma Q10 levels.[32] A new finding was that moderate alcohol drinking, assessed by a questionnaire and serum γ-GT measurement, seemed to increase plasma Q10 levels. We have suggested that this was due to increased hepatic synthesis or tissue damage. However, in cirrhotic patients and in chronic alcoholics, the plasma Q10 levels have been found to be decreased.[52] Taken together, these findings indicate that the liver seems to play an important role in the regulation of plasma and possibly the whole body Q10 status.

Our results showed that age was positively associated with plasma Q10 levels. Previously, a similar association was observed with blood Q10 levels in smaller studies.[53,54] In addition, the increase in plasma Q10 levels following oral

supplementation has been shown to correlate positively with age.[49] These findings suggest that there may be an attenuated need for plasma Q10 in elderly people, and due to that, the previously observed age-based decrease in body total Q10 levels might be a result of ageing, rather than its reason.

Statin treatment was associated with lowered plasma Q10 levels, even after adjusting for other factors presented above. This finding could be partly explained by the fact that most of the statin users were women (eight women, four men). This result supports, however, the previous proposals that statins can decrease plasma Q10 levels.[55,56]

SUMMARY

A single dose of 30 mg has only a marginal effect on plasma Q10 levels. At higher doses, the dose dependent increase of plasma Q10 levels was found to be linear at least up to a daily dose of 200 mg, which resulted in a more than six-fold increase in plasma Q10 levels. Absorption of Q10 varied considerably between subjects, but no difference in the increase of plasma Q10 levels was observed between granular and oil-based preparations. Simultaneous vitamin E supplementation appeared to decrease the absorption of Q10. The mechanism of this phenomenon is unclear and deserves further investigation.

Of the determinants of plasma Q10, it was found that gender, serum cholesterol, serum, γ-glutamyl transferase, serum triglycerides and age were the most important factors which were directly associated with plasma Q10 concentration. The intensity of conditioning exercise and the use of HMG CoA reductase inhibiting agents showed an inverse association. None of the assessed foodstuffs seemed to be associated positively with plasma Q10 levels, including meat and fish.

The supplementation with 90–200 mg of Q10 daily, did not increase the antioxidative capacity of isolated lipoproteins at a high radical flux *in vitro*. However, the observed elevated proportion of plasma ubiquinol of total Q10 might indicate attenuated plasma lipid peroxidation or increased antioxidative capacity at low radical flux conditions *in vivo*.

Supplementation with vitamin E decreased the proportion of plasma ubiquinol of total Q10, which might be evidence in favour of the regeneration of plasma vitamin E by Q10. However, no interaction was observed between these two antioxidants at high radical flux *in vitro*, i.e. simultaneous Q10 supplementation did not increase the antioxidative efficacy of vitamin E, as assessed by measurement of copper-induced LDL oxidation.

In the future clinical trials, the antioxidative efficacy of supplemented Q10 should be retested by proper *in vivo* measurements of lipid peroxidation, such as GC/MS-based plasma hydroxy fatty acids and plasma or urinary F_2-isoprostanes.

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