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ORIGINAL COMMUNICATION

Coenzyme Q_{10} improves blood pressure and glycaemic control: a controlled trial in subjects with type 2 diabetes

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Objective: Our objective was to assess effects of dietary supplementation with coenzyme Q_{10} (CoQ) on blood pressure and glycaemic control in subjects with type 2 diabetes, and to consider oxidative stress as a potential mechanism for any effects.
Subjects and design: Seventy-four subjects with uncomplicated type 2 diabetes and dyslipidaemia were involved in a randomised double blind placebo-controlled 2×2 factorial intervention.
Setting: The study was performed at the University of Western Australia, Department of Medicine at Royal Perth Hospital, Australia.
Interventions: Subjects were randomly assigned to receive an oral dose of 100 mg CoQ twice daily (200 mg/day), 200 mg fenofibrate each morning, both or neither for 12 weeks.
Main outcome measures: We report an analysis and discussion of the effects of CoQ on blood pressure, on long-term glycaemic control measured by glycated haemoglobin (HbA_{1c}), and on oxidative stress assessed by measurement of plasma F_2-isoprostanes.
Results: Fenofibrate did not alter blood pressure, HbA_{1c}, or plasma F_2-isoprostanes. There was a 3-fold increase in plasma CoQ concentration (3.4 ± 0.3 μmol/l, $P < 0.001$) as a result of CoQ supplementation. The main effect of CoQ was to significantly decrease systolic (-6.1 ± 2.6 mmHg, $P = 0.021$) and diastolic (-2.9 ± 1.4 mmHg, $P = 0.048$) blood pressure and HbA_{1c} ($-0.37 \pm 0.17\%$, $P = 0.032$). Plasma F_2-isoprostane concentrations were not altered by CoQ (0.14 ± 0.15 nmol/l, $P = 0.345$).
Conclusions: These results show that CoQ supplementation may improve blood pressure and long-term glycaemic control in subjects with type 2 diabetes, but these improvements were not associated with reduced oxidative stress, as assessed by F_2-isoprostanes.
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Introduction

Coenzyme Q_{10} (CoQ) is a lipid-soluble molecule derived mainly from endogenous synthesis. It plays an essential role as an electron carrier in mitochondrial oxidative phosphorylation (Overvad *et al*, 1999), and may have an important role as an antioxidant (Thomas *et al*, 1999). Our objective here was to determine whether supplementation with CoQ could lower blood pressure and improve glycaemic control in a group of type 2 diabetic subjects. We have also explored oxidative stress as a potential mechanism for any observed effects.

The evidence for a benefit of CoQ on blood pressure is consistent, but limited. Several controlled intervention studies involving hypertensive patients have found that CoQ can lower blood pressure appreciably (Burke *et al*, 2002; Singh *et al*, 1999; Yamagami *et al*, 1986; Digiesi *et al*, 1990). The effect of CoQ on blood pressure in diabetic subjects has

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not been explored. The results of controlled intervention studies that have assessed the effects of CoQ on glycaemic control in diabetic subjects are inconsistent (Singh *et al*, 1999; Eriksson *et al*, 1999; Henriksen *et al*, 1999), and further studies are needed. Supplementation with CoQ can result in the inhibition of LDL oxidisability *ex vivo* (Raitakari *et al*, 2000), but there is little evidence for an effect of CoQ to inhibit oxidative damage *in vivo*.

The present communication is part of a study that was designed to examine the effects of CoQ and fenofibrate on vascular function in type 2 diabetic subjects with dyslipidaemia. An effect of CoQ to improve endothelial dysfunction of the brachial artery in this population has been reported (Watts *et al*, 2002). We have assessed here the effect of CoQ supplementation on blood pressure, on long-term glycaemic control, monitored by measurement of HbA_{1c}, and on oxidative stress assessed by measurement of plasma F_2-isoprostane concentrations.

Methods

Subjects

Eighty subjects, 61 men and 19 women, with type 2 diabetes and dyslipidaemia were recruited from the community. Diabetes was defined as a non-fasting or post standardised oral glucose load plasma glucose concentration >11.1 mmol/l on one occasion, or a fasting plasma glucose >7 mmol/l on two occasions. Dyslipidaemia was defined as fasting serum triglycerides >1.8 mmol/l or HDL <1.0 mmol/l with a total cholesterol <6.5 mmol/l and a total cholesterol : HDL cholesterol ratio >4. Exclusion criteria included age >75 y, body mass index >40 kg/m^2, history of myocardial infarction or stroke, insulin therapy, smoking, macroalbuminuria, serum creatinine >150 μmol/l, abnormal liver or muscle enzymes, use of antioxidants, lipid-regulating therapy, angiotensin-converting enzyme inhibitors and calcium channel blockers, and blood pressure $>160/90$ mmHg. The study was performed at the University of Western Australia, Department of Medicine at Royal Perth Hospital in Perth, Western Australia, Australia. The Royal Perth Hospital Ethics Committee approved the study and all subjects gave written informed consent.

Experimental design

A randomised double-blind placebo-controlled 2×2 factorial intervention of 12 weeks' duration was performed in subjects with uncomplicated type 2 diabetes and dyslipidaemia. Eighty subjects completed the intervention and data were available on all variables of interest for 74 subjects. We report here an analysis and discussion of the main effects of CoQ on glycaemic control, blood pressure and oxidative stress. After a 6-week baseline period during which diet and body weight were monitored, subjects were randomly assigned to one of four groups: (1) 200 mg coenzyme Q_{10} (CoQ, Blackmores Laboratories, Sydney, Australia) and 200 mg fenofibrate (Laboratories Fournier, Dijon, France); (2) 200 mg CoQ and fenofibrate placebo; (3) CoQ placebo and 200 mg fenofibrate; and (4) CoQ placebo and fenofibrate placebo. Coenzyme Q_{10} was taken as 2×50 mg capsules twice daily, and fenofibrate was taken as a single dose of 200 mg in the morning. Matching placebos were used for both CoQ and fenofibrate. Subjects attended the department every 2 weeks to monitor compliance and ensure minimal body weight change.

Blood pressure

Blood pressures were measured at baseline and at the end of intervention using a Dinamap 1846SX/P oscillometric recorder (Criticon Inc., Tampa, Florida, USA). Subjects rested in the supine position for 5 min, then blood pressures and heart rate were measured on the right arm at 2 min intervals. The mean of all blood pressure measurements was calculated. Blood pressures were not disclosed to the subjects during the study.

Biochemistry

Venous blood samples were collected at baseline and at the end of intervention in the morning after a 12 h fast. For those tests not carried out immediately, serum and plasma was frozen at -80°C and thawed immediately prior to analysis. Urine samples were collected at the end of baseline and at the end of the 12 week intervention period. Aliquots of the urine samples were frozen at -80°C and thawed immediately prior to analysis.

Serum total cholesterol, triglycerides and HDL cholesterol were measured using enzymatic colorimetric methods (Boehringer Mannheim, Mannheim, Germnay) on a Hytachi 917 analyser (Hytachi, Tokyo, Japan). High-density lipoprotein cholesterol was measured after precipitation of apolipoprotein B-100-containing particles with dextran sulphate. Low-density lipoprotein cholesterol was estimated by the Friedewald formula and by direct assay when triglycerides were more than 3.5 mmol/l. HbA_{1c} was measured using a commercially available kit employing high performance liquid chromatography (HPLC, BioRad Laboratories, Sydney, Australia). Serum insulin was measured using an automated immuno-enzymometric assay (Tosoh Corp, Kyobashi, Tokyo, Japan). Plasma glucose was measured using Boehringer Mannheim reagents on a Hitachi 917 analyser (Hitachi Ltd, Tokyo, Japan).

Total serum CoQ concentration was measured in a subsample of the group by reverse-phase HPLC using electrochemical detection according to the method of Lang *et al* (1986). F_2-isoprostane concentrations were measured in plasma by gas chromatography-mass spectrometry using negative chemical ionisation (NCI). This method has been previously described in detail (Mori *et al*, 1999; Hodgson *et al*, 1999). Briefly, blood samples were collected into cold tubes containing reduced glutathione and centrifuged within 15 min at 1000 g for 10 min at 4°C. The plasma was

protected from oxidation by addition of 40 μg butylated hydroxytoluene per ml of plasma then stored at −80°C until analysis. The intra-assay coefficient of variation for measurement of F_2-isoprostanes was 8%.

Statistics

Statistical analyses were performed using SPSS 10.0 software (SPSS Chicago, IL, USA). Results are presented as mean (±s.e.m.) and $P<0.05$ was chosen as the level of significance. Analysis of variance was used to determine overall differences between groups at baseline and the Bonferroni test was used *post hoc* where significant differences were found. General linear models were used to examine post intervention main effects of fenofibrate and CoQ after adjustment for baseline values, and after further adjustment for age, sex and body weight. Models including the interaction term of fenofibrate with CoQ were run initially, but because no significant interaction was found for any of the variables, this term was not included in the final models.

Results

The 74 subjects, 58 men and 16 women, who completed this study were aged between 31 and 75 y with a mean age of 53.2±1.0 y. Mean age was not different between groups at baseline, and the distribution of men and women was similar between groups (Table 1). In addition, apart from lower plasma F_2-isoprostane concentrations in the fenofibrate group in comparison to the placebo group ($P=0.020$), there were no significant differences at baseline in any of the measured variables.

The mean baseline and post intervention values for variables considered in subjects in each group are presented in Table 1. Also presented are the *P*-values for main effects of fenofibrate and CoQ analysed as between-group differences in post intervention values after adjusting for baseline values (see statistical methods). There was no interaction between fenofibrate and CoQ for any of these variables. Fenofibrate had a main effect to significantly lower total cholesterol, triglycerides and LDL cholesterol, and significantly increase HDL cholesterol. There was no significant main effect of fenofibrate on other variables.

Coenzyme Q_{10} supplementation resulted in a significant, approximately 3-fold, increase in serum CoQ concentration (3.4±0.4 μmol/l, $P<0.001$). Coenzyme Q_{10} supplementation significantly lowered systolic blood pressure (main effect −6.1±2.6 mmHg, $P=0.021$; Figure 1), and diastolic blood pressure (main effect: −2.9±1.4 mmHg, $P=0.048$). HbA_{1c} was also significantly decreased by CoQ supplementation (main effect −0.37±0.17%, $P=0.032$; Figure 2), but fasting plasma glucose concentrations (main effect 0.14±0.39, $P=0.717$) and fasting serum insulin concentrations (main effect 1.20±1.13, $P=0.290$) were not altered by CoQ. Plasma F_2-isoprostane concentrations were not altered by CoQ supplementation (main effect 0.14±0.15 nmol/l,

Table 1 Mean values at baseline and at the end of intervention for subjects completing the study. Results are means (s.e.m.). Interaction was not significant for any of these variables and *P*-values are shown for main effects of fenofibrate and coenzyme Q_{10} analysed using general linear models as between-group differences in post intervention values after adjusting for baseline values

	Placebo n = 18		*Fenofibrate* n = 18		*Coenzyme Q_{10}* n = 19		*Fenofibrate + coenzyme Q_{10}* n = 19			
Variable	*Baseline*	*Post*	*Baseline*	*Post*	*Baseline*	*Post*	*Baseline*	*Post*	P-*value for fenofibrate*	P-*value for coenzyme Q_{10} main effect*
Males/females (*n*)	13/5		14/4		17/2		14/5			
Age (y)	55.2 (2.3)		53.6 (2.4)		52.3 (1.4)		51.7 (1.6)			
Weight (kg)	87.5 (4.0)	87.9 (4.1)	88.9 (4.2)	87.5 (4.0)	91.2 (2.7)	90.4 (2.7)	88.2 (3.1)	88.7 (3.3)	0.278	0.350
Total cholesterol (mmol/l)	5.3 (0.2)	5.4 (0.2)	5.5 (0.2)	4.7 (0.2)	5.3 (0.2)	5.3 (0.2)	5.2 (0.2)	4.7 (0.2)	< 0.001	0.478
Triglycerides (mmol/l)	2.3 (0.2)	2.7 (0.3)	2.6 (0.3)	1.5 (0.2)	2.2 (0.2)	2.0 (0.2)	3.0 (0.5)	1.9 (0.4)	< 0.001	0.421
LDL cholesterol (mmol/l)	3.3 (0.2)	3.2 (0.2)	3.4 (0.2)	2.9 (0.1)	3.4 (0.2)	3.4 (0.2)	3.0 (0.3)	2.8 (0.2)	0.004	0.177
HDL cholesterol (mmol/l)	1.02 (0.03)	0.98 (0.04)	0.94 (0.04)	1.11 (0.04)	0.94 (0.03)	0.96 (0.04)	0.93 (0.04)	1.07 (0.05)	< 0.001	0.570
Plasma CoQ (mmol/l)[a]	1.19 (0.11)	1.30 (0.14)	1.30 (0.12)	1.23 (0.07)	1.47 (0.09)	4.79 (0.38)	1.33 (0.17)	5.04 (0.77)	0.764	< 0.001
Systolic blood pressure (mmHg)	136.6 (3.7)	137.8 (4.0)	130.4 (4.6)	130.8 (4.3)	127.1 (4.2)	123.2 (3.2)	131.8 (3.5)	127.4 (3.8)	0.726	0.021
Diastolic blood pressure (mmHg)	77.5 (2.2)	80.2 (2.4)	73.5 (1.7)	74.9 (2.0)	75.5 (2.2)	75.2 (2.2)	76.8 (1.7)	75.1 (1.6)	0.246	0.048
HbA_{1c} (%)	6.3 (0.3)	6.6 (0.2)	7.1 (0.4)	7.4 (0.4)	6.9 (0.3)	7.0 (0.3)	7.5 (0.3)	7.2 (0.2)	0.797	0.032
Blood glucose (mmol/l)	7.0 (0.4)	7.2 (0.6)	8.9 (0.9)	8.2 (0.7)	8.5 (0.7)	8.2 (0.6)	8.3 (0.8)	8.0 (0.5)	0.787	0.717
Serum insulin (mU/l)	15.2 (2.3)	14.5 (2.2)	14.8 (2.9)	16.4 (2.9)	12.6 (1.2)	14.2 (1.8)	10.7 (1.2)	13.1 (1.3)	0.223	0.290
Plasma isoprostane (nmol/l)	1.55 (0.13)	1.45 (0.12)	1.01 (0.11)	1.18 (0.09)	1.22 (0.13)	1.37 (0.16)	1.21 (0.11)	1.50 (0.21)	0.564	0.345

[a] $n=9$, $n=11$, $n=11$ and $n=9$ for placebo, fenofibrate, CoQ and fenofibrate + coenzyme Q_{10} respectively.

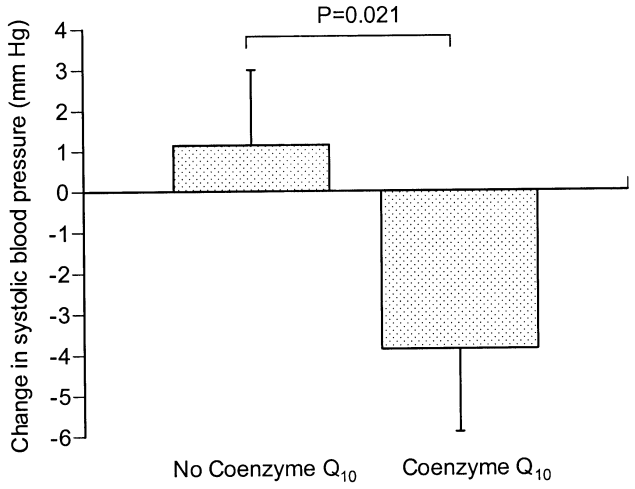

Figure 1 Change in systolic blood pressure for those subjects not taking coenzyme Q_{10} (placebo and fenofibrate groups) and those subjects taking coenzyme Q_{10} (coenzyme Q_{10} and fenofibrate + coenzyme Q_{10} groups, values are mean ± s.e.m.).

$P = 0.345$). Effects of CoQ on systolic blood pressure, diastolic blood pressure and HbA_{1c} remained significant after adjustment for age, sex and body weight.

Discussion

We have investigated here the effects of CoQ supplementation on blood pressure, long-term glycaemic control and lipid peroxidative damage. Subjects involved in this study had high-normal blood pressure and type 2 diabetes with good glycaemic control, although HbA_{1c} was elevated above normal. Supplementation with CoQ resulted in a significantly lower systolic and diastolic blood pressure, and a significant improvement in long-term glycaemic control, monitored by measurement of HbA_{1c}. Coenzyme Q_{10} did not influence oxidative stress, assessed by measurement of plasma F_2-isoprostane concentrations.

Oxidative stress may contribute to raised blood pressure (Kitiyakara & Wilcox, 1998). This may be related to increased production of reactive oxygen species resulting in inactivation of endothelial-derived nitric oxide, increased vascular tone and raised blood pressure (Grunfeld *et al*, 1995).

The evidence that CoQ can lower blood pressure is consistent, but insufficient for any firm conclusions. Previous controlled intervention studies in humans involving small numbers suggest that CoQ supplementation can lower blood pressure in subjects with uncontrolled or poorly controlled hypertension (Singh *et al*, 1999; Yamagami *et al*, 1986; Digiesi *et al*, 1990). In all these studies, where subjects had blood pressures at baseline of $>160/95$, both systolic and diastolic blood pressure fell significantly. Yamagami *et al* (1986) found that CoQ resulted in a fall in blood pressure of 19/6 mmHg in 20 subjects who received 100 mg/day of CoQ or placebo for 12 weeks in a parallel designed study. Digiesi *et al* (1990) found that CoQ resulted in a fall in blood pressure of 11/8 mmHg in 18 subjects who received 100 mg/day CoQ or placebo in a 10-week crossover study. In another study, where 59 hypertensive subjects received 120 mg/day CoQ or placebo for 8 weeks, CoQ resulted in a fall in blood pressure of 15/9 mmHg (Singh *et al*, 1999). In addition, a recent study involving 76 older men and women with isolated systolic hypertension who received 120 mg/day CoQ or placebo for 12 weeks found a significant fall in systolic blood pressure of 18 mmHg (Burke *et al*, 2002). These observed reductions in blood pressure in the range 10–20/5–10 mmHg are remarkable, and if substantiated would be potentially important therapeutically.

In the present study we found a fall in blood pressure of about 6/3 mmHg. These effects of CoQ are less than pre-

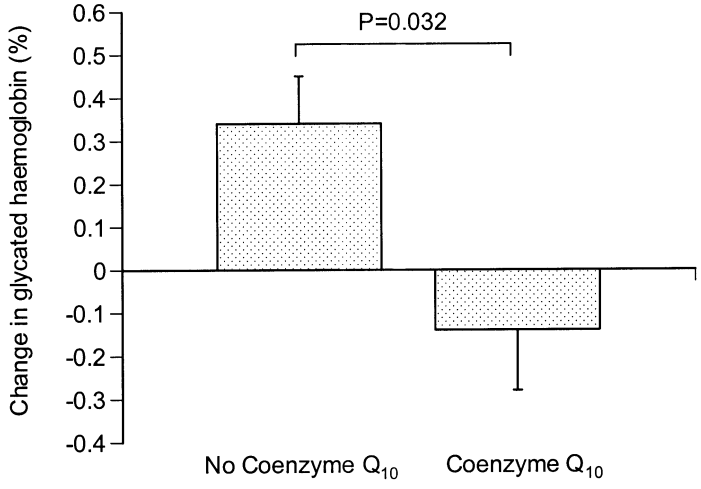

Figure 2 Change in glycated haemoglobin for those subjects not taking coenzyme Q_{10} (placebo and fenofibrate groups) and those subjects taking coenzyme Q_{10} (coenzyme Q_{10} and fenofibrate + coenzyme Q_{10} groups, values are mean ± s.e.m.).

viously reported (Burke *et al*, 2002; Singh *et al*, 1999; Yamagami *et al*, 1986; Digiesi *et al*, 1990), but subjects involved in this study had blood pressures at baseline that were not in the hypertensive range where benefits may be more obvious. Therefore, the results of our study in type 2 diabetics are consistent, although less pronounced than those of previous studies in subjects with hypertension, and suggest that CoQ has the potential to lower blood pressure.

Increasing evidence suggests that individuals with type 2 diabetes are under greater oxidative stress (Bonnefont-Rousselot *et al*, 2000; West, 2000). Oxidative stress and hyperglycaemia may be causally related, with oxidative stress both contributing to and resulting from hyperglycaemia, insulin resistance and deterioration in β-cell function (Ceriello, 2000; West, 2000, McCarty, 1999a). Studies showing that oxygen radical damage is increased and antioxidant defences are reduced in type 2 diabetes suggest that elevated oxidative stress may be due to both increased production of reactive oxygen species and decreased antioxidant concentrations (West, 2000). This provides a theoretical basis for investigation of the effects of CoQ on glycaemic control in diabetes.

Few studies have investigated the effects of CoQ on glycaemic control. A higher serum CoQ has been associated with lower HbA_{1c} cross-sectionally (Jameson, 1991), but results of controlled intervention studies in humans have been inconsistent (Singh *et al*, 1999; Eriksson *et al*, 1999; Henriksen *et al*, 1999). Impressive reductions in fasting blood glucose and insulin concentrations were found with CoQ (120 mg/day) in diabetic hypertensive subjects, but markers of long-term glycaemic control were not monitored in this study (Singh *et al*, 1999). No improvement in HbA_{1c} was found in a study involving 23 type 2 diabetic subjects who received 200 mg/day CoQ or placebo for 6 months (Eriksson *et al*, 1999). Likewise, in 34 type 1 diabetic subjects who received 100 mg/day CoQ or placebo for 3 months, CoQ did not improve long term glycaemic control, assessed using HbA_{1c} (Henriksen *et al*, 1999). In the present study, we found a significant improvement in HbA_{1c}, but found no improvements in fasting blood glucose or insulin concentrations.

The lack of consistent effects of CoQ supplementation on metabolic control in diabetes may relate to differences in several aspects of the studies. The populations recruited to the studies may have differed in drug treatments used, dose of treatments and initial HbA_{1c} concentrations. Sample size may also be an important factor, and with 76 subjects included in the final analysis, the present study is the largest to assess the effect of CoQ on glycaemic control. The effect size may be small, and large sample sizes may be required. A sample size less than 76 subjects would be unlikely to detect an improvement in HbA_{1c} of the magnitude observed in this study. However, further studies are clearly needed to define any benefits of CoQ on glycaemic control in diabetes.

We have also investigated the hypothesis that reduced oxidative stress contributes to, and/or results from, benefits of CoQ on blood pressure and glycaemic control. We have used measurement of plasma F_2-isoprostanes as a marker of oxidative stress *in vivo*. F_2-isoprostanes, which are formed *in vivo* by the non-enzymatic free radical-induced peroxidation of arachidonic acid, are currently believed to be one of the best available markers of lipid peroxidation *in vivo* (Roberts & Morrow, 2000). Measurement of F_2-isoprostanes in plasma can be used to assess endogenous lipid peroxidation, and may provide a reliable indicator of oxidative stress *in vivo* (Roberts & Morrow, 2000; Lawson *et al*, 1999).

Coenzyme Q_{10} might reduce oxidative stress by inhibiting generation of superoxide by mitochondria. This is an effect that may be particularly important in diabetic subjects (Nishikawa *et al*, 2000). Inhibition of oxidative damage in LDL (Thomas *et al*, 1999), improved insulin sensitivity (Bonnefont-Rousselot *et al*, 2000; West, 2000) and β-cell function (McCarty, 1999a) and lower blood pressure (Kitiyakara & Wilcox, 1998) may result in reduced oxidative stress, inhibition of oxidative damage in the arterial wall, and improved glycaemic control and lower blood pressure. We found no effect of CoQ supplementation on plasma F_2-isoprostane concentrations. This result does not support the proposed mechanism, but F_2-isoprostanes are only one marker of oxidative stress. If any effects are specific at the cellular or sub-cellular level, rather than more systemic, then circulating concentrations of F_2-isoprostanes may not change despite any reduction in oxidative stress. Therefore, effects of CoQ on oxidative stress cannot be ruled out. An alternative explanation is that CoQ lowers blood pressure and improves glycaemic control via mechanisms other than oxidative stress.

In diabetes, oxidative stress is maximal post-prandially (Anderson *et al*, 2001). The implications of this study for post-prandial oxidative stress in diabetes require future investigation. Future studies should also focus on the effects of CoQ on glycaemic control in diabetic subjects with poor control and on blood pressure in hypertension.

This study was designed to assess the effects of fenofibrate and CoQ on arterial function and blood lipids, and blood pressure and glycaemic control were secondary endpoints. The population was selected to have dyslipidaemia and vascular dysfunction, and hypertension and impaired glycaemic control were not entry criteria. Effects of CoQ might have been larger in subjects with elevated blood pressure and poor glycaemic control. In addition, because this was a 2×2 factorial study, there was the possibility of effects of fenofibrate. However, because there was no main effect of fenofibrate on blood pressure, glycaemic control and lipid peroxidation, or interaction of CoQ with fenofibrate, we were able to assess the main effects of CoQ.

In conclusion, the results of this study are consistent with the suggestion that supplementation of CoQ lowers blood pressure and improves long-term glycaemic control in type 2 diabetic subjects. However, our results do not provide support for the proposed mechanism involving reduced oxidative stress, as assessed using a marker of lipid peroxidative damage.

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