Coenzyme Q_{10} Improves Endothelial Dysfunction in Statin-Treated Type 2 Diabetic Patients

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OBJECTIVE — The vascular benefits of statins might be attenuated by inhibition of coenzyme Q_{10} (CoQ_{10}) synthesis. We investigated whether oral CoQ_{10} supplementation improves endothelial dysfunction in statin-treated type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — In a double-blind crossover study, 23 statin-treated type 2 diabetic patients with LDL cholesterol <2.5mmol/l and endothelial dysfunction (brachial artery flow-mediated dilatation [FMD] <5.5%) were randomized to oral CoQ_{10} (200 mg/day) or placebo for 12 weeks. We measured brachial artery FMD and nitrate-mediated dilatation (NMD) by ultrasonography. Plasma F_2-isoprostane and 24-h urinary 20-hydroxyeicosatetraenoic acid (HETE) levels were measured as systemic oxidative stress markers.

RESULTS — Compared with placebo, CoQ_{10} supplementation increased brachial artery FMD by 1.0 ± 0.5% ($P = 0.04$), but did not alter NMD ($P = 0.66$). CoQ_{10} supplementation also did not alter plasma F_2-isoprostane ($P = 0.58$) or urinary 20-HETE levels ($P = 0.28$).

CONCLUSIONS — CoQ_{10} supplementation improved endothelial dysfunction in statin-treated type 2 diabetic patients, possibly by altering local vascular oxidative stress.

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Endothelial dysfunction portends diabetic vasculopathy. Endothelial dysfunction reflects increased vascular oxidative stress, whereby uncoupling of endothelial nitric oxide synthase activity and mitochondrial oxidative phosphorylation impairs the bioavailability and action of nitric oxide (1).

Statins are widely used in diabetes management and can reduce cardiovascular events (2). However, a proportion of statin-treated patients remain at risk of cardiovascular disease. Statins inhibit conversion of 3-hydroxy-3-methylglutaryl-CoA to mevalonate, but may thereby also decrease production of other intermediates in the cholesterol biosynthetic pathway, such as coenzyme Q_{10} (CoQ_{10}) (3), an important intracellular antioxidant. We hypothesized that oral CoQ_{10} supplementation would improve endothelial dysfunction in statin-treated type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

— We recruited type 2 diabetic patients aged 40–79 years on stable-dose statin therapy for ≥6 weeks. Inclusion criteria were serum LDL cholesterol <2.5 mmol/l and endothelial dysfunction, defined as brachial artery flow-mediated dilatation (FMD) <5.5%. Exclusions included use of antioxidant supplements or other lipid-regulating medications, GHb >8.5%, and blood pressure >150/90 mmHg.

Eligible subjects were assigned in a double-blind and randomized manner to oral CoQ_{10} (200 mg/day) (Blackmores, Balgowlah, Australia) or placebo for 12 weeks. After a 4-week washout, participants crossed over to the alternate treatment. Brachial artery ultrasonography was performed, and fasting blood and 24-h urine samples were collected at the start and end of each treatment period. The Royal Perth Hospital Ethics Committee approved the study.

The brachial artery was imaged using a 12-MHz transducer connected to an Acuson Aspen ultrasound system (Siemens Medical Solutions, Malvern, PA), and FMD was measured as previously described (4). Endothelium-independent nitrate-mediated dilatation was measured following sublingual administration of glyceryl trinitrate (400 μg). Ultrasound images were analyzed using semiautomated edge-detection software (5).

Total cholesterol, triglycerides, and HDL cholesterol were determined by enzymatic methods, and LDL cholesterol was calculated using the Friedewald equation. GHb was measured using high-performance liquid chromatography. Plasma CoQ_{10} was measured by reverse-phase high-performance liquid chromatography using electrochemical detection (interassay coefficient of variation 14%). Plasma F_2-isoprostane and 24-h urinary 20-hydroxyeicosatetraenoic acid levels (markers of systemic oxidative stress) were measured by gas chromatography-mass spectrometry (interassay coefficients of variation 5.6 and 10%, respectively) (6–8).

Data were analyzed using SPSS 15.0 (Chicago, IL) and SAS 9.1 (Cary, NC). Plasma CoQ_{10} data (skewed distribution) were logarithmically transformed for parametric analysis. Treatment effects were compared using mixed-effects models. Carryover effects were examined for and excluded.

RESULTS — Participants were typically middle-aged (mean ± SD age 68 ± 6 years) and overweight (BMI 29 ± 4 kg/m^2), with satisfactory control of glycemia (GHb 6.9 ± 0.7%), blood pressure (systolic 123 ± 14 mmHg and diastolic 65 ± 7), and lipids (LDL cholesterol 1.8 ± 0.3 mmol/l). Median duration of diabetes was 8 years. Seventy-eight percent of subjects

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had a history of hypertension, 48% had a history of stroke or coronary disease, and 26% had microvascular complications. Eighty-three percent of subjects were taking antihyperglycemic medication, most commonly metformin (78%); 52% were taking ACE inhibitors; 21% were taking angiotensin receptor blockers; and 65% were taking aspirin. Atorvastatin was the most commonly prescribed statin (52%), followed by simvastatin (35%) and pravastatin (13%).

Baseline brachial artery diameter was similar at all assessments and unaltered by CoQ_{10} supplementation (Table 1). CoQ_{10} increased brachial artery FMD by mean ± SEM 1.0 ± 0.5% ($P = 0.04$) compared with placebo but did not alter nitrate-mediated dilatation ($P = 0.66$). Absolute percent FMD pre- and postplacebo, pre- and post-CoQ_{10}, and change in percent FMD with placebo and CoQ_{10} are shown in supplemental Figures A1, A2, and A3 (available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc08-1736/DC1), re- spectively. Despite increasing plasma CoQ_{10} levels 2.7-fold ($P < 0.001$), CoQ_{10} supplementation did not alter plasma F_2-isoprostane ($P = 0.58$) or urinary 20-hydroxyeicosatetraenoic acid levels ($P = 0.28$) or influence glycemia, blood pressure, or lipids ($P > 0.05$).

Table 1—*Effect of placebo and oral CoQ_{10} on arterial function, biochemical variables, and blood pressure*

	Placebo	Oral CoQ_{10}	*P*
Baseline brachial artery diameter (mm)			
Pretreatment	3.9 ± 0.1	3.9 ± 0.1	
Treatment end	3.9 ± 0.1	3.9 ± 0.1	
Change	−0.1 ± 0.0	0.0 ± 0.0	0.69
Brachial artery FMD (%)			
Pretreatment	2.2 ± 0.6	2.2 ± 0.7	
Treatment end	2.1 ± 0.7	3.2 ± 0.5	
Change	0.0 ± 0.5	1.0 ± 0.6	0.04
Brachial artery NMD (%)			
Pretreatment	16.9 ± 1.1	17.3 ± 0.9	
Treatment end	17.8 ± 1.0	17.5 ± 1.0	
Change	0.9 ± 0.9	0.2 ± 0.8	0.66
Plasma CoQ_{10} (μmol/l)			
Pretreatment	0.9 (0.2)	0.8 (0.3)	
Treatment end	0.8 (0.2)	2.2 (1.5)	
Change	0.0 (0.1)	1.2 (1.5)	<0.001
Plasma F_2-isoprostanes (pmol/l)			
Pretreatment	1,302 ± 68	1,284 ± 70	
Treatment end	1,275 ± 86	1,298 ± 69	
Change	−27 ± 55	14 ± 42	0.58
Urinary 20-HETE (pmol/24 h)			
Pretreatment	828 ± 102	831 ± 109	
Treatment end	775 ± 104	888 ± 126	
Change	−53 ± 80	57 ± 117	0.28
GHb (%)			
Pretreatment	7.0 ± 0.1	7.0 ± 0.2	
Treatment end	6.9 ± 0.2	7.0 ± 0.2	
Change	−0.1 ± 0.1	−0.1 ± 0.1	0.58
LDL cholesterol (mmol/l)			
Pretreatment	1.9 ± 0.1	1.7 ± 0.1	
Treatment end	1.9 ± 0.1	2.0 ± 0.1	
Change	0.1 ± 0.1	0.2 ± 0.1	0.41
Systolic blood pressure (mmHg)			
Pretreatment	126 ± 4	122 ± 3	
Treatment end	121 ± 3	121 ± 4	
Change	−4 ± 3	−1 ± 2	0.38
Diastolic blood pressure (mmHg)			
Pretreatment	67 ± 1	64 ± 2	
Treatment end	65 ± 1	66 ± 1	
Change	−2 ± 1	1 ± 1	0.09

Data are means ± SEM or medians (interquartile range). Treatment effects compared using mixed-effects models, with adjustment for baseline, treatment sequence, and period. 20-HETE, 20-hydroxyeicosatetraenoic acid; NMD, nitrate-mediated dilatation.

CONCLUSIONS — The new finding was that CoQ_{10} supplementation improved endothelial dysfunction in statin-treated type 2 diabetic patients, with no alteration in two markers of systemic oxidative stress. This is consistent with our previous study in statin-naive dyslipidemic type 2 diabetic patients in whom oral CoQ_{10} also improved brachial artery FMD but did not alter plasma F_2-isoprostane levels (4). However, a study in coronary heart disease patients (20% with diabetes and 80% statin-treated) showed that oral CoQ_{10} increased both brachial artery FMD and endothelium-bound extracellular superoxide dismutase activity, suggesting that the beneficial effects on endothelial function are related to improvements in local vascular oxidative stress (9). CoQ_{10} could also decrease vascular oxidative stress by recoupling endothelial nitric oxide synthase and/or mitochondrial oxidative phosphorylation. The fact that plasma F_2-isoprostane levels in our diabetic subjects were not significantly different from those in our previously studied nondiabetic control subjects (1,360 ± 74 vs. 1,394 ± 122 pmol/l, respectively; $P = 0.80$) (4) probably reflects their satisfactory glycemic control; our results might have differed had we included patients with greater degrees of hyperglycemia and systemic oxidative stress. Whether CoQ_{10} supplementation might improve endothelial function by modulating other vasoactive mediators, such as endothelin 1 (10) or asymmetric dimethylarginine, (11) merits further investigation.

Our statin-treated subjects had lower plasma CoQ_{10} concentrations compared with those in the statin-naive dyslipidemic type 2 diabetic patients in our previous study (0.8 [0.2] vs. 1.3 [0.6] μmol/l; $P < 0.01$) (4). Although the lowering of plasma CoQ_{10} concentrations with pravastatin therapy was not shown to predict cardiovascular outcomes in coronary patients (12), the effect of pravastatin (40 mg/day) on plasma CoQ_{10} levels was modest (~15% reduction vs. placebo) and inhibition of endogenous CoQ_{10} production may be greater with higher doses of more potent statins (3).

The patients in our study had endothelial dysfunction despite satisfactory control of blood pressure, glycemia, and lipids and may be representative of the proportion of statin-treated patients at increased residual risk of cardiovascular disease. Our absolute improvement in FMD of 1% with CoQ_{10} supplementation may potentially translate to a 10–25% reduction in residual cardiovascular risk in these patients (13,14). Impaired FMD is a consistent predictor of adverse cardiovascular events. Several interventions that improve FMD also improve cardiovascular outcomes (13–15). The significance of the findings in our report, however, requires further investigation in a clinical end point trial.

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