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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 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, double-blind, to oral CoQ_{10} 200mg/day or placebo for 12 weeks. We measured brachial artery FMD and nitrate-mediated dilatation (NMD) by ultrasonography. Plasma F_2-isoprostane and 24-hour 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 (ED) portends diabetic vasculopathy. ED reflects increased vascular oxidative stress, whereby uncoupling of endothelial nitric oxide (eNOS) activity and mitochondrial oxidative phosphorylation impairs the bioavailability and action of nitric oxide (NO). (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-Coenzyme A 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 ED 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 <2.5mmol/L and ED, 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 (BP) >150/90mmHg.

Eligible subjects were randomized, double-blind, to oral CoQ_{10} 200mg/day (Blackmores, Balgowlah, Australia) or placebo for 12 weeks. After 4 weeks washout, participants crossed over to the alternate treatment. Brachial artery ultrasonography was performed and fasting blood and 24-hour urine samples 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 measured as previously described. (4) Endothelium-independent nitrate-mediated dilatation (NMD) was measured following sublingual administration of glyceryl trinitrate 400µg. Ultrasound images were analyzed using semi-automated edge detection software. (5)

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

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

RESULTS

Participants were typically middle-aged (68 ± 6 years) and overweight (BMI 29 ± 4kg/m^2), with satisfactory control of glycemia (GHb 6.9 ± 0.7%), BP (systolic 123 ± 14, diastolic 65 ± 7mmHg) and lipids (LDL-cholesterol 1.8 ± 0.3mmol/L). Median duration of diabetes was 8 years. 78% had a history of hypertension, 48% a history of stroke or coronary disease, and 26% had microvascular complications. 83% were

taking antihyperglycemic medication, most commonly metformin (78%), 52% were taking ACE inhibitors, 21% angiotensin receptor blockers, and 65% 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 1.0 ± 0.5% (p=0.04) compared with placebo, but did not alter NMD (p=0.66); absolute %FMD pre- and post-placebo, pre-and post CoQ_{10}, and change in %FMD with placebo and CoQ_{10} are shown in the online appendix: Figures A1, A2, and A3 (available at http://care.diabetesjournals.org), respectively. 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-HETE levels (p=0.28), nor influence glycemia, BP or lipids (p>0.05).

CONCLUSIONS

The new finding was that CoQ_{10} supplementation improved ED 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-naïve dyslipidemic type 2 diabetic patients, where 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, 80% statin-treated) showed that oral CoQ_{10} increased both brachial artery FMD and endothelium-bound extracellular superoxide dismutase activity, suggesting that the benefits on endothelial function are related to improvements in local vascular oxidative stress. (9) CoQ_{10} could also decrease vascular oxidative stress by recoupling eNOS and/or mitochondrial oxidative phosphorylation. That plasma F_2-isoprostane levels in our diabetic subjects were not significantly different from our previously studied non-diabetic controls (1360 ± 74 vs 1394 ± 122pmol/L, 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 than the statin-naïve 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 (40mg/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 ED despite satisfactory control of BP, glycemia and lipids, which may represent 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, require further investigation in a clinical endpoint trial.

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Table 1. Effect of placebo and oral CoQ_{10} on arterial function, biochemical variables and BP.

		Placebo	Oral CoQ_{10}	p value
Baseline brachial artery	Pre-treatment	3.9 ± 0.1	3.9 ± 0.1	
diameter (mm)	Treatment end	3.9 ± 0.1	3.9 ± 0.1	
	Change	-0.1 ± 0.0	0.0 ± 0.0	0.69
Brachial artery FMD	Pre-treatment	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	Pre-treatment	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}	Pre-treatment	0.9 (0.2)	0.8 (0.3)	
(umol/L)	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	Pre-treatment	1302 ± 68	1284 ± 70	
(pmol/L)	Treatment end	1275 ± 86	1298 ± 69	
	Change	-27 ± 55	14 ± 42	0.58
Urinary 20-HETE	Pre-treatment	828 ± 102	831 ± 109	
(pmol/24hr)	Treatment end	775 ± 104	888 ± 126	
	Change	-53 ± 80	57 ± 117	0.28
GHb	Pre-treatment	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	Pre-treatment	1.9 ± 0.1	1.7 ± 0.1	
(mmol/L)	Treatment end	1.9 ± 0.1	2.0 ± 0.1	
	Change	0.1 ± 0.1	0.2 ± 0.1	0.41
Systolic BP	Pre-treatment	126 ± 4	122 ± 3	
(mmHg)	Treatment end	121 ± 3	121 ± 4	
	Change	-4 ± 3	-1 ± 2	0.38
Diastolic BP	Pre-treatment	67 ± 1	64 ± 2	
(mmHg)	Treatment end	65 ± 1	66 ± 1	
	Change	-2 ± 1	1 ± 1	0.09

Data are mean ± SEM and median (interquartile range).
Treatment effects compared using mixed-effect models, with adjustment for baseline, treatment sequence and period.