

Commentary

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Coenzyme Q₁₀ and diabetic endotheliopathy: oxidative stress and the ‘recoupling hypothesis’

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Summary

Increased oxidative stress in diabetes mellitus may underlie the development of endothelial cell dysfunction by decreasing the availability of nitric oxide (NO) as well as by activating pro-inflammatory pathways. In the arterial wall, redox imbalance and oxidation of tetrahydrobiopterin (BH₄) uncouples endothelial nitric oxide synthase (eNOS). This results in decreased production and increased consumption of NO, and generation of free radicals, such as superoxide and peroxynitrite. In the mitochondria, increased redox potential uncouples

oxidative phosphorylation, resulting in inhibition of electron transport and increased transfer of electrons to molecular oxygen to form superoxide and other oxidant radicals. Coenzyme Q₁₀ (CoQ), a potent antioxidant and a critical intermediate of the electron transport chain, may improve endothelial dysfunction by ‘recoupling’ eNOS and mitochondrial oxidative phosphorylation. CoQ supplementation may also act synergistically with anti-atherogenic agents, such as fibrates and statins, to improve endotheliopathy in diabetes.

Introduction

Cardiovascular disease is the major complication of type 2 diabetes. Its inception relates to endothelial cell dysfunction, or endotheliopathy,¹ with multiple aetiologies that are centrally linked via oxidative stress (Figure 1). Endothelial dysfunction reflects disordered physiology of several endothelium-derived vasoactive factors, in particular nitric oxide (NO). NO is produced in endothelial cells from L-arginine and molecular oxygen under the action of endothelial nitric oxide synthase (eNOS), in a closely-coupled system that involves two important cofactors: nicotinamide adenine dinucleotide phosphate (NADPH) and tetrahydrobiopterin (BH₄) (Figure 2),² and uncoupling of this system results in endothelial dysfunction.^{1–4}

In this article, we briefly review the role of oxidative stress in the pathogenesis of endothelial dysfunction in type 2 diabetes, with specific reference to its effects on NO, and generate the hypothesis that an uncoupling process, affecting both eNOS activity and mitochondrial oxidative phosphorylation, is a key initiator of diabetic endotheliopathy. We develop the notion that supplementation with coenzyme Q₁₀ (CoQ) may potentially reverse or prevent diabetic endotheliopathy by recoupling these two processes. We also discuss the therapeutic potential of CoQ, especially in the context of combination therapy with fibrates and statins. In its broadest sense, we refer to these approaches to correcting endotheliopathy as the ‘recoupling hypothesis’.

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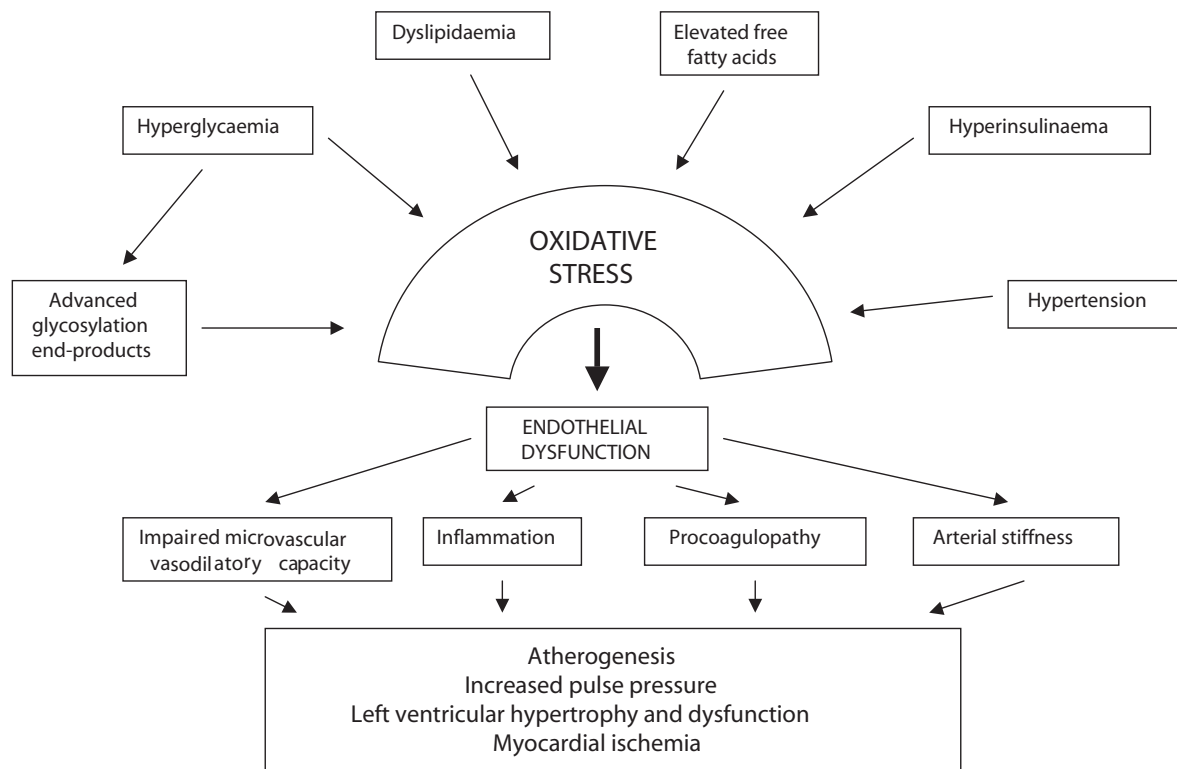


Figure 1. Endothelial dysfunction in diabetes has multiple aetiologies, all of which may act via the common pathway of oxidative stress. This results in disturbance of microvascular autoregulation, activation of pro-inflammatory and pro-thrombotic pathways, and increased arterial stiffness, promoting the development of cardiovascular complications.

Oxidative stress in the arterial wall

Increased oxidative stress reflects the increased generation of free radicals and oxidizing species in relation to antioxidant defences. It may also be viewed as redox imbalance in specific tissues or organ systems. There are several specific biochemical sources of reactive oxygen species (ROS) in vascular cells, including mitochondrial electron transport, xanthine oxidase, cyclooxygenase, NO synthase and NAD(P)H oxidase.⁴ The genesis of ROS essentially involves the production of superoxide by the coupling of electrons to molecular oxygen, and its subsequent reduction to yield hydrogen peroxide and, finally, hydroxyl radicals. Superoxide also reacts with NO to form the reactive nitrogen species (RNS) peroxynitrite, resulting in an amplification pathway for superoxide-mediated oxidative stress or redox imbalance. The metabolism of ROS and RNS is depicted simply in Figure 3.

Accumulation of ROS and RNS impairs several cellular functions directly by oxidizing or nitrosating DNA, proteins and lipids, and indirectly by interacting with proteins containing iron and thionyl groups. This may result in impaired NO signalling, inactivation of mitochondrial oxido-reductases, activation of nuclear factor kappa B (NF- κ B) and

activator protein-1 (AP-1) transcription factors, and enhanced cellular proliferation and inflammation.¹

The precise contribution of the individual enzyme and coenzyme systems to vascular oxidative stress is not entirely known, although there is evidence that the NAD(P)H oxidase system is a major source of superoxide generation in the arterial wall.^{5,6} Mitochondrial electron transport must also play an important role, not only by controlling cellular bioenergetics, but also by regulating the cytosolic concentrations of NADH and NADPH that are the substrates for the corresponding vascular oxidase. CoQ may be critical to the metabolism of ROS and RNS by coupling mitochondrial oxidative phosphorylation (Figure 4a), and this mechanism of action may importantly be altered in diabetes and insulin resistance.^{7,8}

Oxidative stress in diabetes: uncoupling of eNOS and mitochondrial oxidative phosphorylation

Increased oxidative stress in diabetes has been consistently shown in experimental studies,^{5,9}

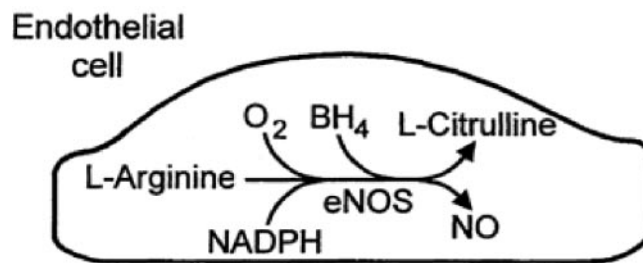
and its primary cause is related to hyperglycaemia. The multiple mechanisms by which hyperglycaemia increases oxidative stress include increased glycosylation of functional proteins, glucose auto-oxidation, activation of the polyol pathway, and uncoupling of both oxidative phosphorylation and eNOS. Glyco-oxidation of glucose generates a series of ROS, including superoxide, hydrogen peroxide and hydroxyl radicals. Increased cellular uptake of glucose increases *de novo* synthesis of diacylglycerol (DAG) and activates protein kinase C (PKC), which induces the production of pro-inflammatory cytokines (via NF- κ B activation) and ROS (by activating NAD(P)H oxidase). Long-term hyperglycaemia increases the formation of advanced glycosylation end-products (AGEs), which can bind to endothelial AGE receptors, also inducing receptor-mediated production of ROS and activation of pro-inflammatory pathways (via NF- κ B). Glucose shunting through the polyol pathway depletes cellular NADPH which, in turn, decreases

glutathione-redox cycling, an important mechanism for scavenging free radicals. Increased polyol pathway activity additionally increases the cytosolic concentration of NADH and the cellular redox potential.

Increased oxidative stress may specifically contribute to eNOS uncoupling in endothelial cells of the arterial wall via oxidation of BH₄, a cofactor which is required for the tight regulation of NO production from L-arginine and molecular oxygen (Figure 2).^{2,3} Uncoupling of eNOS results in decreased production of NO, leading to endothelial dysfunction, and electrons are transferred to molecular oxygen to form oxidant species such as superoxide and peroxynitrite, consuming NO and further increasing oxidative stress.

In diabetes, uncoupling of oxidative phosphorylation may also occur at the mitochondrial level as a consequence of hyperglycaemia and elevated fatty acids.^{7,8} Elevated concentrations of NADH and glycerol-3-phosphate increase delivery of electrons

a) "COUPLED" eNOS



b) "UNCOUPLED" eNOS

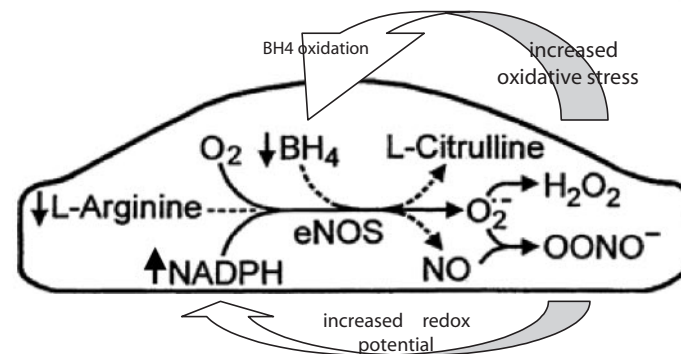


Figure 2. **a** Nitric oxide (NO) is produced from L-arginine and molecular oxygen (O₂) by endothelial nitric oxide synthase (eNOS) in a tightly 'coupled' process involving tetrahydrobiopterin (BH₄) and NADPH. **b** In diabetes, increased redox imbalance (due to increased NADH/NADPH) and decreased availability of BH₄ (due to oxidation) may lead to 'uncoupling' of NO production. This results in transfer of electrons to O₂ to form superoxide (O₂⁻). Superoxide in turn reacts with and consumes NO, to form the oxidant species peroxynitrite (OONO⁻). Hence, oxidative stress is further increased and endothelial function compromised. Coenzyme Q₁₀ (CoQ) may act to scavenge oxidant species, thereby reducing oxidative stress and resulting in 'recoupling' of eNOS. Adapted from reference 2.

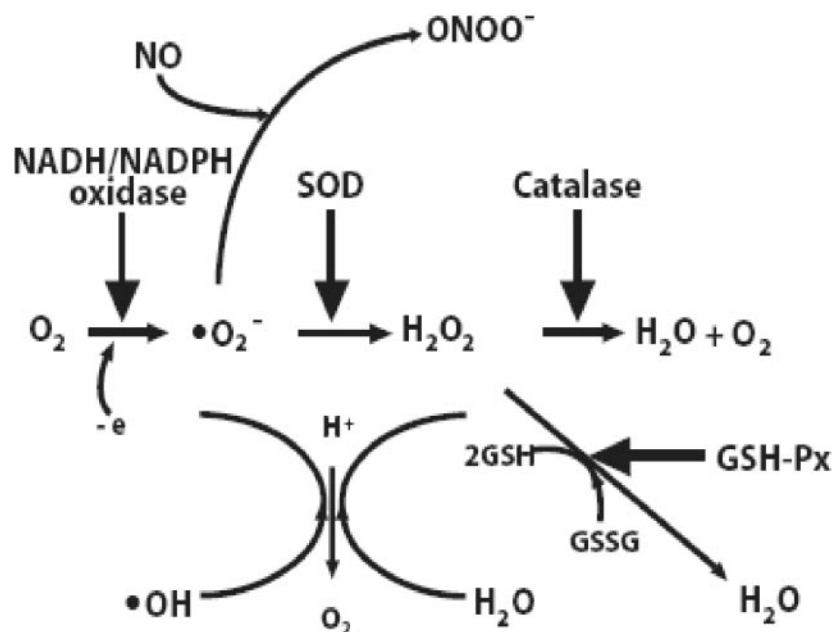


Figure 3. Metabolism of reactive oxygen species (ROS) in the vascular wall. The vascular oxidases (NADH/NADPH oxidase) induce oxidative stress by producing superoxide ($\bullet O_2^-$), which converts nitric oxide (NO) to peroxynitrite ($ONOO^-$). Superoxide dismutase (SOD) has a relative antioxidant effect by converting $\bullet O_2^-$ to hydrogen peroxide (H_2O_2), which is further metabolized to water (H_2O) by catalase and glutathione peroxidase (GSH-Px). Diabetes increases the production of $\bullet O_2^-$ and impairs its metabolism to H_2O . Adapted from reference 4.

to complexes of the respiratory chain via the key intermediate CoQ, leading to inhibition of electron transport at complex III. Uncoupling of oxidative phosphorylation and electron transport results in inefficient generation of adenosine 5'-triphosphate (ATP) by mitochondria and increased transfer of electrons to molecular oxygen, with increased production of superoxide radicals (Figure 4b).

As well as the increased generation of ROS and RNS, reductions in tissue concentration of antioxidants, in particular vitamin E, superoxide dismutase and catalase, have also been demonstrated in diabetic subjects. Thus, decreased antioxidant defences also compound overall oxidative stress in diabetes.

At a cellular level, oxidative stress in diabetes is directly cytotoxic by oxidizing DNA, proteins and lipids, as well as by activating pro-inflammatory and pro-atherogenic intracellular signalling pathways, such as NF- κ B, PKC and mitogen-activated protein (MAP) kinase.¹⁰ These signalling pathways not only uncouple oxidative phosphorylation and eNOS activity, but also aggravate insulin resistance and its vascular complications.

Beyond hyperglycaemia itself, additional clinical factors that contribute to endothelial cell dysfunction in diabetes include dyslipidaemia, hypertension, inflammation, insulin resistance and elevated plasma concentration of asymmetrical dimethylarginine.^{1,9} The pathogenic mechanisms also probably

involve oxidative stress and the uncoupling of both NO production and mitochondrial oxidative phosphorylation, but insulin resistance, dyslipidaemia and elevated plasma non-esterified fatty acid levels may all also have direct inhibitory effects on eNOS activity.^{9,11} These mechanisms will not be discussed further, except to indicate that in diabetic dyslipidaemia, small dense low-density lipoprotein (LDL) particles are highly susceptible to oxidative and nitrosative modification, and a low high-density lipoprotein (HDL)-apoA1 level has a pro-oxidant effect. Hence, these atherogenic effects of LDL and low HDL are compounded by increased oxidative stress in diabetes.

Regulation of oxidative stress and endotheliopathy in diabetes: antioxidants and the therapeutic potential of CoQ

The observation that oxidative stress is increased in diabetes, and contributes to endothelial dysfunction, has generated the notion that antioxidants and other regulators of oxidative stress may protect against and reverse diabetic vasculopathy. While epidemiological studies suggest that conventional antioxidant vitamins (such as vitamin E or α -tocopherol) can potentially decrease the incidence

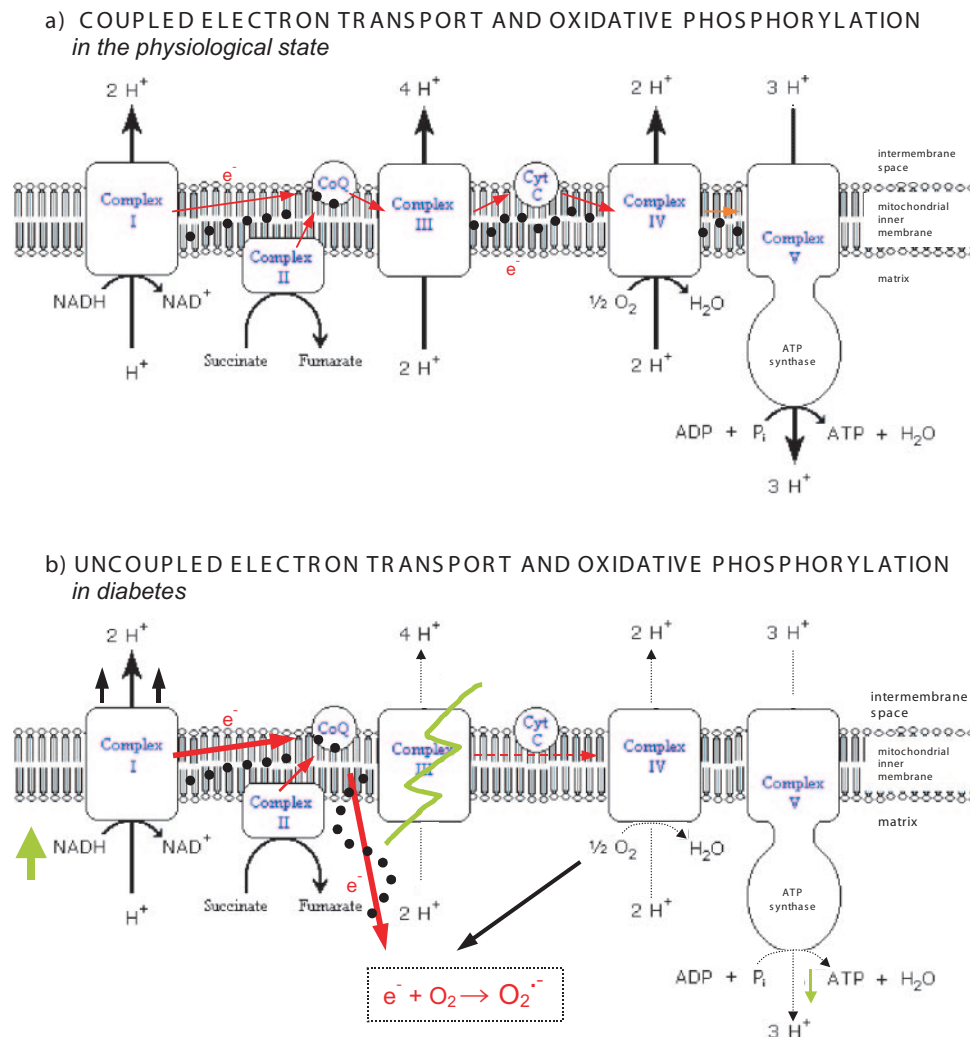


Figure 4. **a** Electron (e^-) transfer through the mitochondrial respiratory chain complexes is coupled to the generation of a transmembrane chemiosmotic proton (H^+) gradient, which drives cellular energy production (ATP, adenosine 5'-triphosphate). Coenzyme Q₁₀ (CoQ) is an important cofactor in facilitating electron transport from complexes I and II to complex III. **b** In diabetes, hyperglycaemia increases the supply of electron donors, such as NADH, which generates a high mitochondrial membrane potential, inhibiting electron transport at complex III. Electron transport and oxidative phosphorylation are uncoupled, resulting in inefficient ATP generation and transfer of electrons to molecular oxygen (O_2) to form superoxide ($O_2^{\cdot-}$) and other free radicals. A quantitative or functional deficiency in CoQ, in the presence of increased electron donors, exacerbates uncoupling of these two processes. Cyt C, cytochrome c. Adapted from Miller KJ. *Metabolic Pathways of Biochemistry*, George Washington University; 1998. [<http://www.gwu.edu/~mpb/oxidativephos.htm>].

of cardiovascular disease, the evidence from controlled clinical trials, which included subjects with diabetes, is less impressive.^{12,13}

Human studies examining the effect of conventional antioxidants on endothelial function of the peripheral circulation in diabetes (based on plethysmography or ultrasonography) have yielded inconsistent results. In patients with type 2 diabetes, there is evidence both for and against an effect of vitamin E supplementation in improving the vasodilator function of forearm resistance arteries in response to acetylcholine.^{14,15} One positive study using the vitamin E analogue, Raxofelast, was not

placebo-controlled and only studied a small number of patients.¹⁴ However, vitamin E supplementation did not improve forearm microcirculatory function in a well-designed controlled study of a larger sample of type 2 diabetic patients.¹⁵ Improvement in methacholine-mediated vasodilator function of forearm resistance arteries has also been reported in subjects with type 2 diabetes following intra-arterial administration of vitamin C,¹⁶ but again the study was small and not placebo-controlled. Intra-arterial administration of the powerful antioxidant α -lipoic acid has been reported to improve forearm blood flow responses to acetylcholine in subjects with

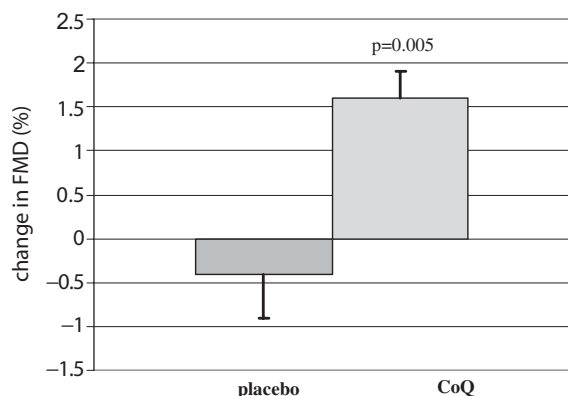


Figure 5. Change in flow-mediated dilatation (FMD) of the brachial artery in diabetic patients treated with placebo or Coenzyme Q₁₀ (CoQ) supplementation (200 mg daily) for 12 weeks. Means \pm SEM. Data from reference 18.

type 2 diabetes,¹⁷ with the greatest benefit seen in those with low plasma concentration of CoQ. This supports an important role of CoQ in endothelial dysfunction in type 2 diabetes.

We recently showed that oral CoQ supplementation improved endothelial function of the brachial

artery in dyslipidaemic patients with type 2 diabetes¹⁸ (Figure 5). We have also reported that the combination of CoQ and fenofibrate, a PPAR- α agonist, has a synergistic effect in improving endothelium-dependent and independent function of forearm resistance arteries in similar patients¹⁹ (Figure 6). These two studies suggest that CoQ may have therapeutic potential in protecting against and reversing vascular disease.

Coenzyme Q₁₀: structure, function, significance in diabetes

CoQ, or ubiquinone, is a lipid-soluble benzoquinone with a side-chain of 10 isoprenoid units (Figure 7), endogenously synthesized in the body from phenylalanine and mevalonic acid. The biological importance of CoQ relies on its role in energy transduction in the mitochondria, where it accepts electrons from several donors (including NADH, succinate and glycerol-3-phosphate) and transfers them to the cytochrome complex system.^{20,21} According to Mitchell's Chemiosmotic Theory, electron transport generates a proton gra-

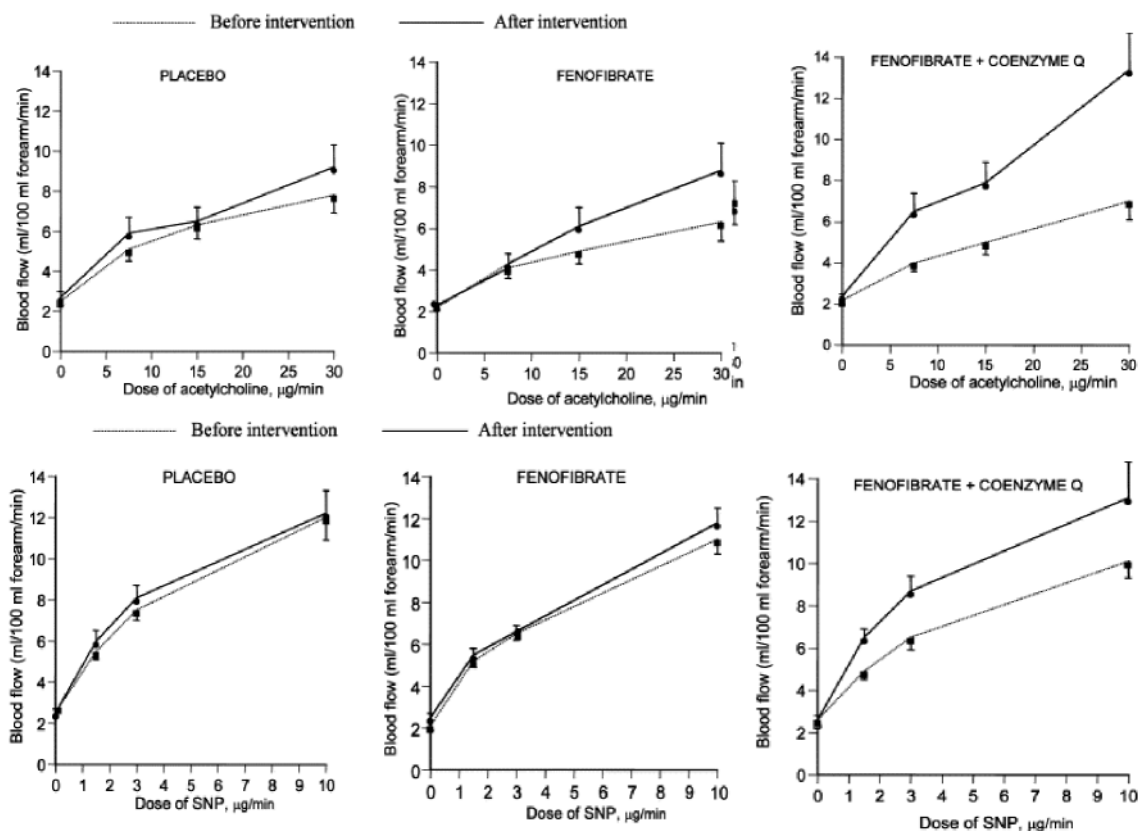


Figure 6. Forearm blood flow responses to **a** acetylcholine and **b** sodium nitroprusside (SNP) in patients treated with placebo, fenofibrate 200 mg daily, and fenofibrate + Coenzyme Q (200 mg + 200 mg daily) for 12 weeks. Data from reference 19.

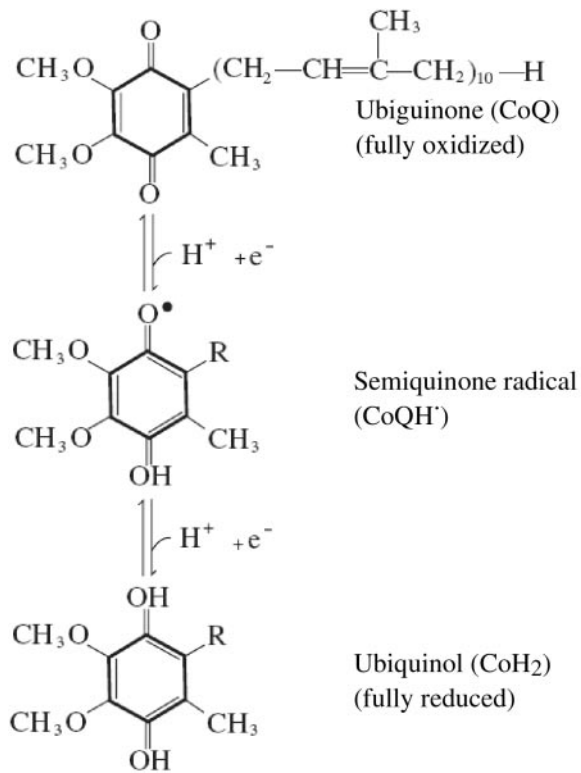


Figure 7. Oxidized coenzyme Q₁₀ (CoQ) or ubiquinone, is reduced to ubiquinol (CoQH₂) by acquiring 2 protons and 2 electrons. CoQ is freely diffusible in the inner mitochondrial membrane, and it couples electron flow to proton movement in mitochondria, a unique property of this small, hydrophobic molecule. It is rate-limiting for electron transfer reactions. R = isoprenoid side chain.

dient across the mitochondrial membrane that, in turn, drives the synthesis of ATP. CoQ is freely diffusible in the inner mitochondrial membrane, shuttling electrons between the less mobile complexes of the chain. Its special property is that it is both an electron and proton transporter, and hence it is critical in coupling electron flow to proton movement²² (Figure 7).

CoQ is also a potent antioxidant and free radical scavenger,²³ as well as a membrane stabilizer. Importantly, this membrane-stabilizing property may be related to its role in extra-mitochondrial electron transfer in plasma membranes. CoQ is a more powerful antioxidant than vitamin E, and is able to inhibit its pro-oxidant activities.²⁴ CoQ supplementation both increases LDL CoQ concentration and inhibits the oxidizability of LDL *ex vivo* in humans.²⁵ CoQ decreases markers of lipid peroxidation *in vivo* in apolipoprotein E gene knockout mice,²⁶ and also inhibits the development of experimental atherosclerosis in rabbits.²⁷

Quantitative or functional deficiency in CoQ may potentially occur in diabetic patients as a consequence of increase in the cytosolic redox potential that overdelivers electrons into the mitochondrial transportation system and uncouples the production of ATP. An absolute or relative deficiency in CoQ could result in a dysfunctional increase in transfer of electrons to molecular oxygen. The mitochondria then become a source of superoxide radical overproduction (Figure 4).

As well as impairing endothelial function, mitochondrial CoQ deficiency may be involved in the pathogenesis of type 2 diabetes by depressing β -cell function,⁶ and mitochondrial dysfunction has also been linked with the development of insulin resistance.⁸ Plasma CoQ concentrations have been reported to be negatively correlated with poor glycaemic control and with diabetic complications, and some clinical trials have also shown that CoQ supplementation can improve glycaemic control and blood pressure in patients with diabetes^{28,29} (Figure 8). Hence, correction of quantitative or qualitative abnormalities in CoQ could have diverse therapeutic benefit on vasculopathy in diabetic patients.

CoQ supplementation and endothelial function

The case for the role of CoQ supplementation in treating and preventing cardiovascular disease in general has been well emphasized in several reviews.^{30–32} Clinically significant CoQ deficiency cannot be corrected by increased dietary intake and requires specific supplementation in the range 100–200 mg CoQ daily. The long-term safety and tolerability of CoQ supplementation has been consistently confirmed in several published animal and human trials,^{30,31} with the only potential drug interaction recorded to date being antagonism of the action of warfarin due to the vitamin-K-like properties of CoQ.

The results of CoQ supplementation studies in rodent models are consistent with a benefit of CoQ on endothelium-dependent arterial relaxation. Yokoyama *et al.* showed that, in comparison with controls, rats pre-treated with CoQ had a 12% improvement bradykinin-induced coronary vasorelaxation after cardiac ischaemia perfusion, and an 18% improvement after intracoronary hydrogen peroxide perfusion ($p < 0.05$).³³ That CoQ decreased maximal free radical burst in the early period of reperfusion suggested a direct protective antioxidant effect. In senescent rats that received dietary CoQ supplementation over 8 weeks, Lonnrot *et al.*

demonstrated improved mesenteric arterial ring relaxation response to isoprenaline *in vitro*, compared with controls ($p=0.0001$).³⁴ In both studies, the vasorelaxation response to sodium nitroprusside (endothelium-independent) was unchanged.

The effects of CoQ on arterial function have also been investigated in controlled intervention studies in human subjects, although only a few studies have been reported to date. Raitakari *et al.* studied 12 healthy hypercholesterolaemic subjects with endothelial dysfunction who received oral CoQ 150mg daily or placebo for 4 weeks in a double-blind crossover study, and showed that CoQ did not significantly alter post-ischaeamic vasodilator function of the brachial artery (4.3% vs. 5.1%, $p=0.99$), measured by ultrasound.³⁵ In a study by our group,¹⁸ 40 patients with type 2 diabetes and endothelial dysfunction were randomised to receive oral CoQ 200mg daily or placebo for 12 weeks. Flow-mediated dilatation of the brachial artery was increased by 66% with CoQ supplementation relative to placebo (absolute change in FMD +1.6% vs. -0.4%, $p=0.005$) (Figure 5), but post-treatment responses remained lower than in healthy controls. CoQ supplementation did not improve nitrate-mediated dilatation of the brachial artery, again suggesting no effect on endothelium-independent vasorelaxation. The reasons for the inconsistent results in the above two studies are unclear, but it is possible that the mechanism by which CoQ affects endothelial function is different in individuals with diabetes compared with hypercholesterolaemic, non-diabetic subjects.

Synergistic effects of CoQ: peroxisome proliferator-activated receptor alpha (PPAR- α) activation

The effects of CoQ on microcirculatory function of the forearm resistance arteries have also been investigated using venous occlusion strain-gauge plethysmography.¹⁹ In a randomized placebo-controlled study of type 2 diabetic patients with endothelial dysfunction, we found that the addition of CoQ 200 mg daily to fenofibrate 200 mg daily over a treatment period of 12 weeks had a synergistic effect in improving both endothelium-dependent and -independent forearm blood flow responses to intra-arterial vasodilator infusion (Figure 6). An additive effect of fenofibrate and CoQ has also been found on brachial artery vasodilator function in type 2 diabetic patients (Watts 2003, unpublished).

Fenofibrate belongs to a class of compounds called fibrates, which activate PPAR- α . PPARs are orphan nuclear receptors that control the expression of key genes involved in the regulation of metabolism, inflammation and thrombosis.^{36–38} Upon ligand activation, PPARs regulate transcription by heterodimerization with the 9-cis retinoic acid receptor and binding to PPAR response elements within the promoter region of target genes. The alpha isoform (PPAR- α) is chiefly expressed in fatty-acid-oxidizing tissues, but also in endothelial and vascular smooth muscle cells and arterial wall macrophages. PPAR- α activation may improve endothelial function in diabetes through diverse mechanisms and pathways,³⁸ including correction of dyslipidaemia and reduction in the expression of adhesion molecules, tissue factor, interleukin-6 and endothelin-1. Activation of PPAR- α can also decrease cellular inflammation and oxidative stress by inhibiting AP-1 and NF- κ B signalling pathways.

The compound effect of CoQ and fenofibrate in improving arterial dysfunction in different arterial beds in type 2 diabetes may involve a favourable co-activation of PPAR- α in endothelial and vascular smooth muscle cells (B. Staels 2003, personal communication). The potential effect of CoQ on PPAR- α activation may partly be due to decreased oxidation and/or nitrosation of this nuclear hormone receptor. An important consequence of this may be synergistic inhibition of the expression of NF- κ B and AP-1,^{19,36,37} with a corresponding depression in cellular proliferation and inflammation. These cellular effects of CoQ and fenofibrate may be associated with improvements in glycaemic control, and result in a reduction in arterial blood pressure.^{28,29} This is an exciting therapeutic potential for CoQ, given that fibrates alone have been shown to decrease cardiovascular events³⁹ and progression of atherosclerosis in type 2 diabetic patients.⁴⁰

CoQ supplementation and statin therapy: enhancing the effects on diabetic endotheliopathy?

As well as having the potential to augment the benefits of PPAR- α agonists on vascular dysfunction, CoQ supplementation may also act synergistically with other anti-atherogenic agents, such as statins. However, the rationale with statins is different, in that it relates to their potential to decrease the intracellular synthesis of CoQ.⁴¹ Statins inhibit HMG-CoA reductase and the formation of farnesyl pyrophosphate, which is essential for the synthesis of the isoprenoid subunits of CoQ. Normal levels

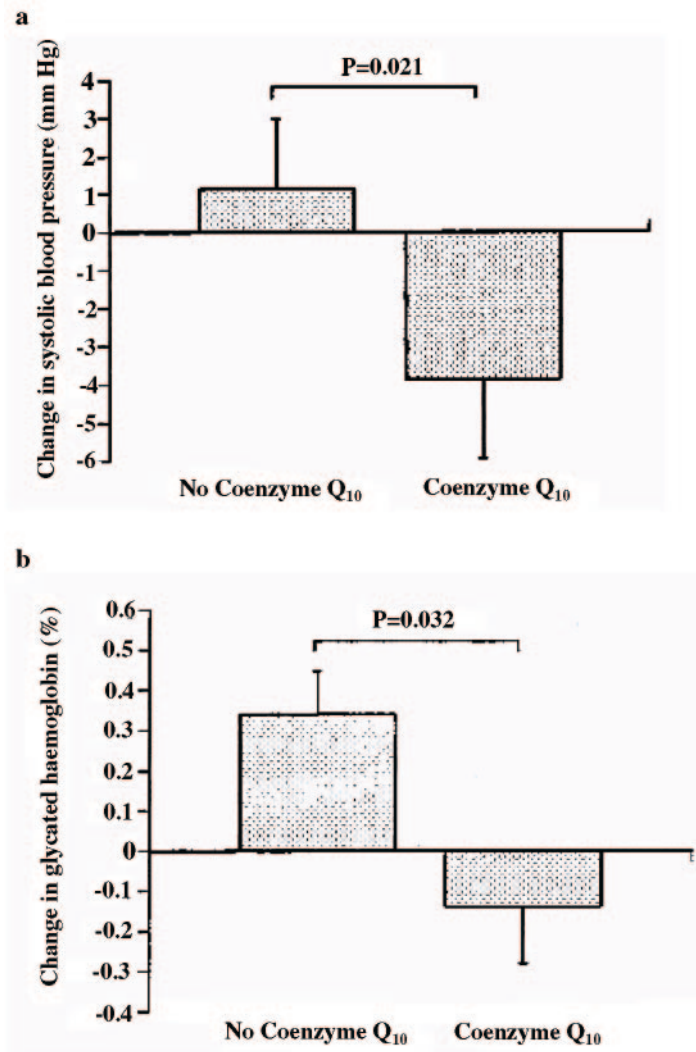


Figure 8. Change in **a** systolic blood pressure (mmHg) and **b** glycated haemoglobin (%) for those subjects not taking coenzyme Q₁₀ (placebo and fenofibrate 200 mg daily groups) and for those subjects taking coenzyme Q₁₀ (coenzyme Q₁₀ 200 mg daily and fenofibrate + coenzyme Q₁₀ groups) after 12 weeks of treatment. Means±SEM. Data from reference 29.

of CoQ in mitochondrial membranes are below those required for kinetic saturation,^{21,22} so that a small reduction in its synthesis could have an important impact on cellular bioenergetics and mitochondrial production of superoxide radicals. This may be particularly important in type 2 diabetes, given that there are data showing that atorvastatin does not consistently improve endothelial function in type 2 diabetes.⁴² Statins can lower plasma CoQ levels independent of an LDL-cholesterol lowering effect,^{43,44} (Figure 9), although in non-diabetics, simvastatin does not appreciably decrease the antioxidant capacity of LDL.⁴⁵ In experimental animals, simvastatin, but not pravastatin, has been reported to decrease myocardial CoQ levels and worsen mitochondrial respiration during ischaemia.⁴⁶ Nevertheless, the full potential of statins to improve vascular function and

decrease the incidence of cardiovascular disease may be offset by a relative reduction in mitochondrial CoQ levels, especially in diabetes. Given that a significant number of diabetic patients still need to be treated with statins to prevent vascular events in clinical trials,^{13,47,48} the notion of whether CoQ supplementation can enhance the clinical benefits of statins in diabetes merits further investigation. We propose that the concepts developed here concerning the 'recoupling hypothesis' provide a good rationale for such further research.

Conclusions: testing the 'recoupling hypothesis'

Type 2 diabetes increases oxidative stress, and this may be central to the development of endothelio-

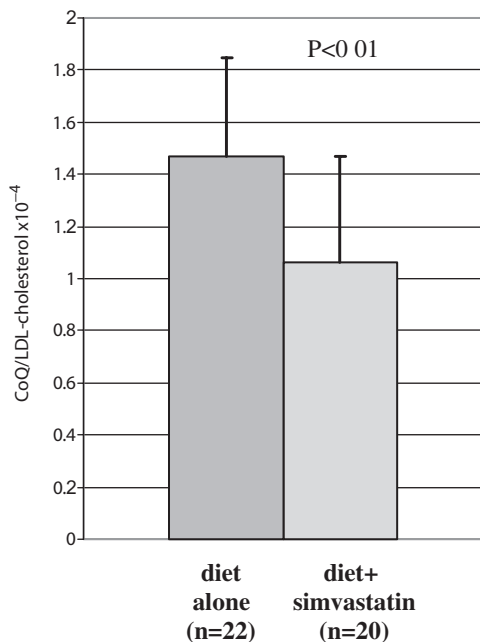


Figure 9. Plasma CoQ:LDL-cholesterol ratio in hyperlipidaemic subjects on diet therapy alone compared with hyperlipidaemic subjects treated with diet plus simvastatin. Mean values \pm SD. Data from reference 43.

pathy. Relative CoQ deficiency may occur in diabetes as a consequence of changes in mitochondrial substrate utilization and an increase in cellular redox potential. CoQ, as a critical intermediate of the mitochondrial electron transport chain and also a potent antioxidant, has the ability to regulate oxidative stress and endothelial function by coupling both mitochondrial oxidative phosphorylation and eNOS activity. Recent reports in type 2 diabetic patients suggest that CoQ supplementation may improve abnormal endothelial function in conduit arteries and augment the benefits of a PPAR- α agonist on microcirculatory dysfunction, possibly by co-activation of this nuclear receptor. CoQ supplementation has also been reported to improve blood pressure and hyperglycaemia in type 2 diabetes, and hence may exert beneficial anti-atherogenic effects through a number of different mechanisms.

Beyond NO, diabetic vasculopathy also involves the pathological effects of endothelin-I and angiotensin II on vascular oxidative stress, vasotonicity and cellular proliferation^{1,6} and whether CoQ also plays a role in regulating the effects of these molecules requires examination. In addition to improving endothelial function, the benefits of CoQ supplementation in diabetes may extend to cardiac function,^{30–32,49} with multiple myocardial and

extramyocardial mechanisms of ventricular systolic and diastolic dysfunction that could potentially be correctable with CoQ. This is especially relevant to the recent demonstration that subjects with well-controlled type 2 diabetes have altered myocardial energy metabolism.^{50,51}

However, the benefits of CoQ supplementation may best be seen in clinical trials involving diabetic subjects who have not yet developed established vascular complications, a notion similar to that proposed by Steinberg to test the effects of conventional antioxidants on atherosclerosis.⁵² Although multiple risk factor modification has recently been shown to be cost-effective treatment for type 2 diabetic patients with established complications,⁵³ demonstrating the cardiovascular benefits of CoQ in such patients, on treatment with several drugs, may be more difficult in clinical trials. However, the effects of CoQ supplementation merit particular examination in diabetic patients on treatment with statins, since these agents may specifically decrease the biosynthesis of CoQ. CoQ may also potentially enhance the therapeutic effects of ACE inhibitors, angiotensin II receptor agonists, insulin sensitizers, and newer agents such as PKC inhibitors. The preliminary experimental and clinical studies on the effects of CoQ supplementation in diabetes reviewed here require testing in clinical endpoint trials, including patients within the wider spectrum of the metabolic syndrome.

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