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# Endothelial control of vascular tone in diabetes mellitus

**L. Poston**

St. Thomas' Hospital, London, UK

The vascular endothelium in diabetes mellitus has a reduced capacity for the synthesis of vasodilators and produces abnormally raised levels of vasoconstrictors and procoagulants. These functional defects could underlie many of the vascular disorders of diabetes [1, 2]. Much attention is now focused upon mechanisms contributing to endothelial dysfunction, and to the development of new treatment strategies based on prevention or reversal of endothelial damage.

The first indication of endothelial malfunction is often the detection in the plasma of a biochemical marker of endothelial cell disruption or activation, including von Willebrand's factor, endothelin or tissue plasminogen activator. An early indication of an abnormal dilatory response is the presence of reduced maximal dilatory capacity which occurs in the microcirculation prior to the onset of the disease in non-insulin-dependent diabetes mellitus (NIDDM). A similar defect is manifest in established insulin-dependent diabetes (IDDM). Reduced physical distensibility is likely to play some role, but recent work has established that reduced synthesis, or sensitivity to endothelial derived nitric oxide (NO) may be contributory. Technically, evaluation of endothelial dilator function is relatively more simple when using preparations of larger vessels and a wealth of evidence now supports the suggestion that the endothelium in diabetes has a reduced capacity to synthesize NO, which may lead to local vasoconstriction and that this is compounded by an increase in endothelin release and, possibly, constrictor prostanoid synthesis.

*Corresponding author:* Professor L. Poston, Department of Obstetrics and Gynaecology, St. Thomas' Hospital, London, SE1 7EH, UK

*Abbreviations*: NIDDM, Non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; NO, nitric oxide AGE, advanced glycation end-products.

In vitro techniques have generally assessed endothelial function in isolated arteries by determination of dilator responses to agonists, e.g. acetylcholine and bradykinin, which stimulate NO synthesis, and by inhibition of NO synthase with arginine analogues, e.g. L-nitro arginine methyl ester. Most of the early studies used preparations of conduit arteries from animal models of diabetes [1], but recent work has concentrated upon the technique of small vessel myography [3] which facilitates the use of 'resistance' arteries (diameter approximately $< 350\ \mu m$) and has enabled studies of isolated small arteries from human biopsy material. In vivo estimates of endothelial dilator capacity in diabetic patients have also been achieved using forearm venous occlusion plethysmography and, more recently, with high resolution ultrasound to visualize conduit artery responses to flow (a physiological stimulus to NO synthesis) [4]. While conclusions are somewhat variable, these different methodological approaches have all pointed to a defect in endothelial control of vascular tone in diabetes.

The vascular endothelium is disadvantaged by physical proximity to the blood, rendering it prone to attack by the metabolic byproducts of diabetes. Many of these could compromise endothelial cell viability and function; indeed it would be surprising if endothelial function were to remain normal [2]. In early IDDM, the elevation of glucose may enhance NO release from the endothelium and contribute to an increase in blood flow. In turn this will increase blood flow and shear stress. The high level of shear in early diabetes in itself could contribute by mechanical means to endothelial cell damage. Prolonged hyperglycaemia may also cause biochemical dysfunction. Stimulation of the polyol pathway may deplete the endothelial cell of NADPH and glutathione. NADPH is a cofactor for NOS III (the endothelial isoform of NO synthase) and glutathione, an antioxidant,

would normally protect the cell against free radical damage. Glucose also increases diacylglycerol and protein kinase C activity which, in turn, may reduce NOS III activity. In the long term, the most damaging aspect of abnormal glucose metabolism is likely to be the accelerated synthesis of advanced glycosylation end products (AGE). AGE effectively reduce NO availability by 'quenching' free NO and, through glycosylation, render low density lipoproteins (LDLs) more susceptible to free radical attack, thus promoting the formation of the oxidized (LDLs). Oxidized LDLs may cause endothelial damage and reduce NO synthesis.

While serum LDL levels are often quantitatively normal in diabetes, there is evidence that qualitative changes occur. The LDL total lipid: apolipoprotein (b) ratio is reduced in IDDM and NIDDM, reflecting an increase in small dense LDLs. These are more susceptible to free radical damage. In addition, the preponderance of linoleic acid in the LDLs in NIDDM also promotes oxidation [5]. These observations are obviously relevant to the increased atherogenic potential of diabetic subjects, but are also pertinent to endothelial damage in the smaller arteries.

The vasculature of the diabetic patient, through reduced cellular antioxidant status and increased LDL susceptibility to oxidation is a target for free radical attack. Free radical synthesis may be enhanced through autoxidation of glucose, glucose induced stimulation of the cyclooxygenase pathway and synthesis of reactive oxygen products by lipids and carbohydrates once they themselves become oxidised. Numerous studies have evaluated oxidative stress in diabetic subjects (see [6, 7] for review); by measurement of the serum levels of the non-enzymatic antioxidants vitamin E, vitamin C and glutathione; by the determination of enzymatic antioxidant pathways, e.g. superoxide dismutase and glutathione peroxidase and by the measurement of the products of oxidation, e.g. oxidised LDLs. The literature presents a confusing picture. Animal models of uncontrolled IDDM show abundant evidence of oxidative stress but in the diabetic patient vitamin E has been described as normal, abnormal or raised. The most consistent finding is a reduction in cellular glutathione. Despite methodological problems in the assessment of lipid oxidation products, many studies now suggest an increase in lipid peroxide synthesis, including a recent description of the presence of 8-epi-prostaglandin $F_{2\alpha}$, an isoprostane [8]. The isoprostanes are omit oxidation products of arachidonic acid with biological activity including vasconstrictor properties.

Interest now centres on a possible role for antioxidants in the treatment/prevention of diabetic angiopathies. Animal studies have shown antioxidants effect reversal of vascular endothelial dysfunction in vitro and treatment with vitamin E has improved neuronal blood flow and vascular endothelial function in conduit arteries. Vitamin E can in itself act as a prooxidant under some circumstances and can also scavenge NO. In a recent study from our laboratory, we have found that vascular endothelial function deteriorated in diabetic animals given vitamin E supplementation. This is not the first report to suggest that vitamin E can be deleterious and some caution should be heeded in the use of high-dose vitamin E supplements. Although several clinical trials of vitamin E supplementation have now been carried out, none has specifically investigated endothelial dilator function, although a group of IDDM patients have shown reduced platelet aggregation while taking vitamin E. Vitamin C supplements have improved glycaemic control in NIDDM and a recent investigation has reported an increase in vasodilator function in the forearm circulation of NIDDM patients after the acute infusion of vitamin C.

In conclusion, dysfunction of endothelium dependent vasodilator dysfunction in diabetes could be a common underlying problem in retinopathy, neuropathy and ischaemia and contribute to the increased risk of atherosclerosis of diabetes. Improved glycaemic control will undoubtedly have benefit, but long-term clinical trials are required to determine whether antioxidant supplementation may prove an effective therapeutic strategy.

## References

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