# Endotheliopathy Precedes Type 2 Diabetes

The recognition that the endothelium is not a passive lining layer of blood vessels but plays a vital role in the maintenance of blood fluidity, vessel wall tone, and permeability has led to an appreciation that endotheliopathy is central to many vascular diseases, including atherosclerosis and diabetic microangiopathy. In this context, the paper by Anastasiou et al. (1) is of considerable interest, for it suggests that there may be evidence of endothelial dysfunction in normoglycemic subjects prone to the future development of type 2 diabetes—that is, women with a history of gestational diabetes. Compared with women known to have been normoglycemic during pregnancy, women with a history of gestational diabetes exhibited impaired flow-mediated dilatation (FMD) in the brachial artery, a response that depends on intact endothelial function and in which the vasodilator nitric oxide (NO) is generated in response to increased shear stress on the vessel wall (2).

Although the significance of vascular changes in an artery that is notable for the absence of atherogenic change may be questioned, such impaired responses have been correlated with impaired endothelium-dependent vasodilatation in coronary arteries in several studies (3,4). The mechanisms underlying endothelial dysfunction cannot be ascertained from such observations, but several possibilities bear consideration. First, the abnormal vascular responses could represent the legacy of the period of hyperglycemia during pregnancy. Studies of the endothelium-dependent vasodilatation in resistance arteries in the forearms of healthy subjects have demonstrated that high glucose concentrations administered acutely intra-arterially may impair the response (in the presence of octreotide to block hyperglycemia-induced insulin release), an effect that cannot not be explained in terms of the osmotic load such exposure represents (5). Nonetheless, one would intuitively expect endothelial function to be rendered near normal if glucose levels were normalized, a concept that appears more acceptable with the recent demonstration that improved glycemic control retards the development of diabetic angiopathy in type 2 diabetes (6) as well as type 1 diabetes. Furthermore, in a few subjects, the abnormality was shown to persist >1 year after delivery, and presumably after the resumption of normal glucose tolerance, and in our own studies, defects in microvascular vasodilatory reserve have been observed in normoglycemic women an average of 8 years after the gestational diabetes.

An alternative explanation is that the disturbance in endothelial function represents the impact of some other feature of the insulin resistance syndrome (IRS), which persists in the absence of dysglycemia. As the authors point out, women with a history of gestational diabetes continue to exhibit evidence of dysmetabolism (7) commensurate with insulin resistance. Although no robust measures of insulin resistance were made in the study reported, the lipid pattern and higher urate level are consistent with such a state. Hypertension, which is commonly associated with insulin resistance, is also associated with endothelial dysfunction (8), which is demonstrable even in secondary forms of hypertension and may improve as blood pressure is lowered (9). However, in the study by Anastasiou et al. (1), there were no significant differences in the blood pressure values of the nonobese women who had a history of gestational diabetes and also exhibited impaired FMD, although the obese cohort did have higher systolic and diastolic blood pressure values.

Lipid disturbances, too, may impair endothelial function (10), with oxidized LDL appearing to have a particularly harmful effect (11). Furthermore, acute effects of a high-fat meal on FMD have been demonstrated (12), perhaps implicating free fatty acids, an adverse response that appears to be blocked by vitamin C (13), which suggests a role for oxidative stress. As with hypertension, there is emerging evidence that improvement in dyslipidemia through the use of pharmacological agents (14), or diet and exercise, may improve endothelium-dependent vasodilatation.

Thus, there is increasing evidence that a panoply of seemingly minor abnormalities that characterize early insulin resistance is associated with endothelial dysfunction, and in some instances, the relationship appears to be causal. Before accepting that the endothelial defect is totally secondary to such extrinsic abnormalities, aggravated by lifestyle changes such as smoking, obesity, and inactivity, one needs to consider the alternative concept that endothelial dysfunction could be a common antecedent (15) or intrinsically linked to many key features of the IRS. Testing such a hypothesis requires a crystal ball, i.e., the capacity to identify people who will develop the clinical features of the IRS (which are known to be associated with endothelial dysfunction) before the earliest manifestations emerge. Type 2 diabetic patients' first-degree relatives are also at risk of developing type 2 diabetes. Despite normoglycemia, such individuals may exhibit evidence of impaired endothelium-dependent microvascular and macrovascular vasodilatation (16), although they, too, may already have other metabolic disturbances that accompany insulin resistance (17).

In recent years, it has become clear that there is a link between low birth weight and the subsequent risk of type 2 diabetes, hypertension, and atherosclerosis in later life (18). The concept that the common cause of these conditions might be intrauterine programming in response to malnutrition has recently been challenged; the alternative view is that the small baby and the insulin-resistant adult represent two phenotypes of an insulin-resistant genotype (19). Regardless of the origin of the link, the study of individuals who had a low birth weight, before insulin-resistant features emerged could provide a means of challenging the concept of intrinsic endotheliopathy.

Leeson et al. (20) studied FMD in 333 school children between 9 and 11 years of age and observed a positive correlation with birth weight that remained after correction for conventional cardiovascular risk factors. Blood pressure, plasma glucose, and plasma lipids did not differ between the children with low birth weight and those with high birth weight except for a small reduction in

HDL cholesterol in the former group. In a more recent study, Martin and Norman (21) described impaired microvascular endothelium-dependent vasodilatation occurring 3 days after birth in infants of low birth weight compared with control subjects of normal birth weight.

The possibility thus emerges that endothelial dysfunction may be intrinsic to the insulin-resistant state, although compounded by certain clinical features of the condition. Several possible mechanisms for such an intimate association have been proposed, including a generalized change in cell membrane biophysical properties that might, for example, alter the presentation of insulin and shear receptors (22), or the impact of intracellular oxidative stress (23). One mechanism that has received direct experimental support from a study of animal models of insulin resistance is the involvement of a cell signal transduction mechanism that is common both to insulin-mediated glucose uptake by cells and to NO generation.

King and colleagues (24) have demonstrated that defects in the IRS-2-phosphatidylinositol 3-kinase pathway may explain the concurrence of insulin resistance and reduced NO bioavailability in the fatty Zucker rat, and the challenge for clinical scientists is to determine whether similar defects are demonstrable in insulin-resistant humans. Nonetheless, it needs to be appreciated that endothelium-dependent vasodilatation is impaired in response to stimuli other than insulin (i.e., shear and agonists such as acetylcholine) that rely on the integrity of other signal transduction pathways.

In conclusion, the study by Anastasiou et al. (1) provides important clues that endothelial dysfunction may antedate type 2 diabetes. The endothelium possesses myriad roles, and it is important that we resist drawing a conclusion from abnormalities in one sphere. Nevertheless, it appears that endothelium-dependent vasodilatation is at least an early abnormality. There is emerging evidence that part of the abnormality described by Anastasiou et al. (1) may be fundamental in nature, although this evidence is compounded by the clinical features that characterize IRS. It is likely that a fuller understanding of the origins of atherosclerosis will rely on elucidation of the nature of this intrinsic component.

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## References

1. Anastasiou E, Lekakis JP, Alevizaki M, Papamichael CM, Megas J, Souvatzoglou A, Stamatelopoulos SF: Impaired endothelium-dependent vasodilatation in women with previous gestational diabetes. *Diabetes Care* 21:2111–2115, 1998
2. Joannides R, Haefeli WE, Linder L, Richard V, Bakkali EH, Thuillez C, Luscher TF: Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. *Circulation* 91:1314–1319, 1995
3. Neunteufl T, Katzenschlager R, Hassan A, Klaar U, Schwarzacher S, Glogar D, Bauer P, Weidinger F: Systemic endothelial dysfunction is related to the extent and severity of coronary artery disease. *Atherosclerosis* 129:111–118, 1997
4. Lieberman EH, Gerhard MD, Uehata A, Selwyn AP, Ganz P, Yeung AC, Creager MA: Flow-induced vasodilation of the human brachial artery is impaired in patients <40 years of age with coronary artery disease. *Am J Cardiol* 78:1210–1214, 1996
5. William SB, Goldfine AB, Timimi FK, Ting HH, Roddy M, Simonson D, Creager M: Acute hyperglycaemia attenuates endothelium-dependent vasodilation in humans in vivo. *Circulation* 97:1695–1701, 1998
6. U.K. Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
7. Ryan EA, Imes S, Liu D, McManus R, Finegood DT, Polonsky KS, Sturis J: Defects in insulin secretion and action in women with a history of gestational diabetes. *Diabetes* 44:506–512, 1995
8. Rossi M, Taddei S, Fabbri A, Tintori G, Credidio L, Virdis A, Ghiadoni L, Salvetti A, Giustic C: Cutaneous vasodilation to acetycholine in patients with essential hypertension. *J Cardiovasc Pharmacol* 29:406–411, 1997
9. Taddei S, Virdis A, Mattei P, Salvetti A: Vasodilation to acetylcholine in primary and secondary forms of human hypertension. *Hypertension* 21:929–993, 1993
10. Voors AA, Oosterga M, Buikema H, May JF, Grandjean JG, van Buiten A, van Gilst WH: Dyslipidaemia and endothelium-dependent relaxation in internal mammary arteries used for coronary bypass surgery. *Cardiovasc Res* 34:568–574, 1997
11. Kugiyama K, Kerns SA, Morrisett JD, Roberts R, Henry PD: Impairment of endothelium-dependent arterial relaxation by lysolecithin in modified low-density lipoproteins. *Nature* 344:160–162, 1990
12. Vogel RA, Corretti MC, Plotnick GD: Effect of a single high-fat meal on endothelial function in healthy subjects. *Am J Cardiol* 79:350–354, 1997
13. Plotnick GD, Corretti MC, Vogel RA: Effect of antioxidant vitamins on the transient impairment of endothelium-dependent brachial artery vasoactivity following a single high fat meal. *JAMA* 278:1682–1686, 1997
14. Simons LA, Sullivan D, Simons J, Celemajer DS: Effects of atorvastatin monotherapy and simvastatin plus cholestyramine on arterial endothelial function in patients with severe primary hypercholesterolaemia. *Atherosclerosis* 137:197–203, 1998
15. Pinkney J, Stehouwer C, Coppack S, Yudkin J: Endothelial dysfunction: cause of the insulin resistance syndrome. *Diabetes* 46 (Suppl. 2):S9–S13, 1997
16. Balletshofer B, Rittig K, Enderle M, Volk A, Maerker M, Pfohl M, Rett K, Haring HU: Disturbed flow-associated brachial artery dilation in glucose tolerant, insulin-resistant first-degree relatives of subjects with type 2 diabetes (Abstract). *Diabetologia* 35 (Suppl. 1): 1212, 1998
17. Humphriss DB, Stewart MW, Berrish TS, Barriocanal LA, Trajano LR, Ashworth LA, Brown MD, Miller M, Avery PJ, Alberti KG, Walker M: Multiple metabolic abnormalities in normal glucose tolerant relatives of NIDDM families. *Diabetologia* 40:1185–1190, 1997
18. Barker DJP, Hales CN, Fall CHD, Osmond C, Phipps K, Clark PMS: Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia* 36:62–67, 1993
19. Hattersley AT, Beards F, Ballantyne E, Appleton M, Harvey R, Ellard S: Mutations in the glucokinase gene of the fetus result in reduced birth weight. *Nat Genet* 19:268–270, 1998
20. Leeson CPM, Whincup PH, Cook DG, Donald AE, Papacosta O, Lucas A, Deanfield JE: Flow-mediated dilation in 9- and 11-year-old children. *Circulation* 96:2233–2238, 1997
21. Martin H, Norman M: Endothelial dysfunction in newborn infants small for gestational age: implications for adult hypertension? (Abstract) *J Vasc Res* 35 (Suppl. 2):P41, 1998
22. Tong P, Thomas T, Bernish T, Humphriss D, Barricoconal L, Stewart M, Walker M, Wilkinison R, Alberti KG: Cell membrane dynamics and insulin resistance in non-insulin-dependent diabetes mellitus. *Lancet* 345:357–358, 1995

23. Tribe RM, Poston L: Oxidative stress and lipids in diabetes: a role in endothelium vasodilator dysfunction? *Vasc Med* 1:195–206, 1996
24. Jiang Z, Lin Y-W, Clermont A, Iragashi M, King G: Direct demonstration of selective insulin resistance on PI 3-kinase pathway in vascular tissues of obese Zucker (fa/fa) rats (Abstract). *Diabetes* 46 (Suppl. 1):54A, 1997