Endothelial Dysfunction: Cause of the Insulin Resistance Syndrome

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Insulin resistance has been proposed as the metabolic basis of atherogenesis. This hypothesis is based on the concept of the "insulin resistance syndrome," according to which insulin resistance is viewed as the primary abnormality that gives rise to dyslipidemia, essential hypertension, impaired glucose tolerance, and NIDDM. However, this hypothesis takes no account of the well-established and central role of vascular endothelium in the atherogenic process. Although endothelial injury is an early and prominent feature of atherogenesis, relatively little attention has been given to its metabolic consequences. In subjects with NIDDM, we have shown that endothelial dysfunction is associated with insulin resistance, raising the question of whether this relationship could be causal. In this article, we review the factors that are considered to be responsible for the development of endothelial dysfunction during atherogenesis, together with the metabolic consequences of endothelial dysfunction. While dysfunction of the endothelium in large and medium-sized arteries plays a central role in atherogenesis, we argue that dysfunction of peripheral vascular endothelium, at arteriolar and capillary level, plays the primary role in the pathogenesis of both insulin resistance and the associated features of the insulin resistance syndrome. We propose that the insulin resistance syndrome, together with many aspects of atherogenesis, can be viewed as the diverse consequences of endothelial dysfunction in different vascular beds. This new and testable hypothesis accounts for both the endothelial and metabolic abnormalities associated with atherogenesis. *Diabetes* 46 (Suppl. 2):S9–S13, 1997

A primary role has been proposed for insulin resistance both in the etiology of the clustering of cardiovascular risk factors and in the pathogenesis of atherosclerotic vascular disease (1). However, it is disputed whether insulin resistance is the primary defect. Endothelial dysfunction is an early and prominent event in atherogenesis. What, then, is its relationship with insulin resistance syndrome? In this article, we argue that endothelial dysfunction is not simply a consequence but is the root cause of most features of the insulin resistance syndrome, in addition to playing a central role in atherogenesis.

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LPL, lipoprotein lipase; vWF, von Willebrand factor.

ENDOTHELIAL DYSFUNCTION, ATHEROSCLEROSIS, AND INSULIN RESISTANCE

Individuals with atherosclerosis exhibit both endothelial dysfunction and impaired insulin action. The endothelium plays an important role in the regulation of hemostasis, blood flow, maintenance of vascular architecture, and mononuclear cell transmigration—all of primary significance in atherogenesis. The endothelium also transports small molecules, macromolecules, and hormones such as insulin and degrades lipoprotein particles. Could endothelial dysfunction contribute to the individual components of the insulin resistance syndrome?

Origins of endothelial dysfunction. Non-denuding, functional endothelial injury and activation are early events in atherogenesis (2). Both primary endothelial injury (the "response to injury hypothesis" of Ross et al. [3]) and primary subendothelial retention of atherogenic lipoproteins (the "response to retention hypothesis" of Williams and Tabas [4]) have been proposed as the initiating factors in atherogenesis. Both hypotheses place endothelial dysfunction at the center of the atherogenic process. The synthesis and secretion of endothelial cell products and adhesion molecules are known to be strongly influenced by a variety of cytokines, components of oxidized lipoproteins, and fluid shear stress (5–10). At the in-vivo level, endothelial cell products can be measured in the circulation, with altered levels potentially reflecting preclinical endothelial activation and dysfunction. Thus, circulating concentrations of von Willebrand factor (vWF) are raised in subjects with a variety of cardiovascular risk markers (11–13) and in cigarette smokers (14). Concentrations of thrombomodulin are also increased in subjects with established atherosclerosis (15). The measurement of other circulating products, such as the adhesion molecules E-selectin, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and CD-31 (8), may offer further means of detecting endothelial activation much earlier in the atherogenic process. The primary origin of these circulating markers is likely to be peripheral capillary endothelium, as opposed to large arterial endothelium, on the basis of the far greater surface area of the former. Thus, free radicals, oxidized lipoproteins, cigarette smoking, and fluid shear stress all likely contribute to endothelial dysfunction.

Consequences of endothelial dysfunction. While endothelial dysfunction in large arteries, brought about by many of the above mechanisms, plays an increasingly recognized and dynamic role in the atherothrombotic process

(16), we propose that endothelial dysfunction in metabolically important capillary beds may be the principal explanation for the development of the insulin resistance syndrome in parallel with large-artery atherosclerosis.

Capillary endothelial dysfunction might play an important role in the evolution of atherogenic changes in lipoprotein concentrations, through impaired action of endothelial-bound lipoprotein lipase (LPL). LPL is the proximal and rate-limiting enzyme-hydrolyzing triglyceride from apolipoprotein B containing lipoprotein particles. Its physiological site of action is at the capillary endothelial cell surface, bound to glycosaminoglycans. Studies in transgenic mice and in subjects with mutations in the LPL gene suggest that LPL dysfunction leads to increased plasma triglycerides, reduced concentrations of HDL cholesterol, and perhaps premature atherosclerosis (17). We propose that a variety of different insults at the capillary endothelial level, including damage from cigarette products, free radicals, oxidized lipoproteins, and shear stress, may cause a loss of glycosaminoglycan and LPL at the endothelial cell surface, in turn resulting in reduced access of triglyceride-rich lipoprotein particles to LPL. Thus, an endothelial hypothesis could explain why the dyslipidemia of the insulin resistance syndrome is confined to triglycerides and HDL cholesterol.

In resistance vessels, endothelium regulates blood flow and blood pressure through the production of the powerfully vasoactive substances nitric oxide, endothelin-1, and thromboxane A2 (18). Endothelium also regulates vascular architectural remodeling through production of platelet-derived growth factor-β and transforming growth factor-β (19). Hypertension, through increased shear stress in large arteries and arterioles, may not only initiate endothelial injury, but the resulting defective vasodilatation and vascular remodeling are likely to sustain and further aggravate the hypertension.

The endothelium is a key regulator of hemostasis and fibrinolysis, controlling the activities of the intrinsic pathway and the fibrinolytic and protein-C anticoagulant pathways, as well as influencing platelet activation and vasomotion. Thus, endothelial dysfunction is a plausible explanation for the increased levels of plasminogen activator inhibitor-1 that are observed in subjects with insulin resistance syndrome and with cardiovascular disease (20,21) and that may further contribute to vascular damage.

Microalbuminuria is a powerful risk factor for cardiovascular disease in both diabetic (22,23) and nondiabetic subjects (24), and it is linked closely to the insulin resistance syndrome (25–27), although the mechanism for this association is poorly understood. Microalbuminuria has come to be viewed as a local renal consequence of a more generalized vascular endothelial dysfunction, with its development being antedated by the appearance of increased levels of vWF in both IDDM (28) and NIDDM subjects (29), which raises the possibility that generalized capillary and arteriolar endothelial dysfunction explains the relationship of microalbuminuria with insulin resistance and the insulin resistance syndrome.

Thus, many aspects of the insulin resistance syndrome may be explained as consequences of endothelial dysfunction in different vascular beds. What, then, is the relationship between endothelial dysfunction and insulin resistance?

Role of the endothelium in insulin action. Endothelium plays an important role in the regulation of blood flow to insulin-sensitive tissues and the delivery of insulin to the interstitium. Thus, we propose that endothelial dysfunction is an important factor in the pathogenesis of insulin resistance.

Insulin acts as a vasodilator, and in insulin-resistant states, including obesity, hypertension, and NIDDM, impaired insulin-mediated increase in skeletal muscle blood flow has been described (30). Furthermore, insulin-resistant subjects have reduced skeletal muscle capillarization (31,32). Thus, both reduced capillary surface area and impaired capillary endothelial function, along with a failure of endothelial vasodilator response to insulin in arterioles, could contribute to insulin resistance through delayed delivery of the hormone to the interstitial fluid.

Other studies have highlighted the importance of the capillary endothelium in the transport of insulin from the vascular to the interstitial compartment. Jansson et al. (33) demonstrated that the endothelium is a barrier to insulin and that changes in plasma insulin concentrations are followed by slower changes in interstitial insulin. Studies in dogs suggest that a major determinant of insulin action during stepped hyperinsulinemic clamps is the delay in transendothelial insulin transport (34). Insulin-resistant humans also show delay in the delivery of insulin to the interstitial space (35). It is clear that resistance at the tissue level makes an additional contribution to insulin resistance, as in steady-state studies the interstitial insulin concentration is not the main determinant of insulin action. In the dynamic state, as insulin levels change, active or passive transendothelial insulin transport assumes greater importance, with a rate-limiting step before insulin binding to its receptors (36).

Thus, the endothelium has important roles both in the delivery of insulin to the tissues and as a target for insulin action. Both reduced endothelial surface area and dysfunction of the available endothelium may make major contributions to insulin resistance, with poor skeletal muscle capillarization perhaps increasing the vulnerability of certain individuals to further deterioration in insulin action consequent on endothelial damage (31,32). In this way, physical integrity and normal function of the arteriolar and capillary endothelia are prerequisites for normal insulin action.

Endothelium and cigarette smoking. The most powerful risk factor for atherosclerotic vascular disease is cigarette smoking. Cigarette smoking is also toxic to the endothelium (37) and causes a dose-related impairment of flow-mediated vasodilatation (38). Smoking causes a reversible increase in insulin resistance (39), reduces levels of HDL cholesterol, and increases postprandial triglyceridemia (40). Therefore, we propose that arteriolar and capillary endothelial dysfunction may be the proximal cause for many of the metabolic defects associated with cigarette smoking, while toxic effects on the large vessels may play a more direct role in atherothrombosis.

Endothelium and hypercholesterolemia. Hypercholesterolemia is also a powerful risk factor for vascular disease. It is also associated with impaired endothelium-dependent vasodilatation (41) but not with the insulin resistance syndrome. We suggest that hypercholesterolemia leads predominantly to large-vessel endothelial damage and atherogenesis, with less effect at the arteriolar level and little or no effect on capillary endothelium. We suggest that this distribution of endothelial damage is such that pure hypercholesterolemia is able to cause large-vessel atherosclerosis without giving rise to accompanying features of the insulin resistance syndrome.

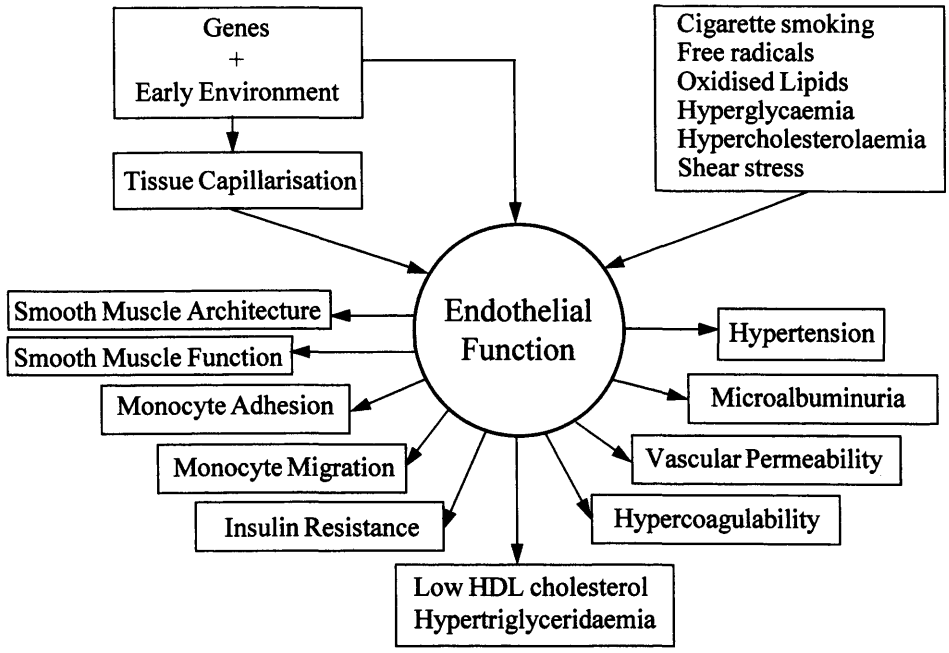

FIG. 1. Determinants of endothelial function and consequences of endothelial dysfunction.

TOWARD A NEW HYPOTHESIS

It is plausible, on the basis of these observations, that arteriolar and capillary endothelial dysfunction are mechanistically linked to insulin resistance. What evidence supports the view that endothelial dysfunction in these sites is involved in the pathogenesis of both the cluster of risk factors and insulin resistance?

Endothelial dysfunction is central to the insulin resistance syndrome. Endothelial behavior is altered both in patients with established atherosclerotic disease and in those with insulin resistance syndrome risk factors but without overt atherosclerosis. A range of abnormalities of capillary flow and pressure have been documented in various capillary beds in subjects with essential hypertension (42), impaired glucose tolerance, and NIDDM (43), consistent with the presence of capillary endothelial dysfunction. In two large population studies, increased levels of vWF, reflecting capillary endothelial activation, were associated with hypertriglyceridemia and low levels of HDL cholesterol (44,45). Again, abnormal endothelial function, rather than being a consequence, may play a primary role in the pathogenesis of insulin resistance syndrome.

Insulin resistance is related to endothelial dysfunction. There are cogent reasons to suppose that endothelial function and insulin action are linked. In two epidemiological studies (44,45) concentrations of vWF were correlated with those of insulin—a surrogate marker for insulin resistance in population studies of nondiabetic subjects. However, no direct association between insulin resistance and circulating markers of endothelial dysfunction has been demonstrated.

To explore this question, we examined the relationship between circulating levels of vWF and insulin action in a group of 33 subjects (25 men, 8 women) with NIDDM who were aged 56.1 ± 1.3 years (mean ± SD), with BMI 29.0 ± 0.9 kg/m^2, HbA_1 10.1 ± 2.3%, diabetes duration 5.0 (1.0–23.0) years [median (range)], and albumin excretion rate 9.5 (0.2–119.3) μg/min. Ethical approval was granted by the institutional ethical committee, and written informed consent was obtained from each subject. Statistical analyses were performed with Statistical Package for Social Sciences (SPSS). Positively skewed data were logarithmically transformed, parametric tests were used throughout, and two-tailed P values were determined. Blood pressure was recorded with a mercury sphygmomanometer, from the nondominant arm, in the sitting position, after 5 min rest. The mean of three measurements was calculated. Twenty subjects had blood pressure >160/90, and 10 subjects on antihypertensive drugs were taken off medication for 4 weeks. Subjects attended in the fasting state for venesection and measurement of insulin resistance. Insulin resistance was determined using an insulin sensitivity test (46) and calculated as glucose infusion rate/steady-state plasma glucose. Levels of vWF antigen correlated with the metabolic clearance rate of glucose (r = –0.35, P = 0.05), with HDL cholesterol (r = –0.36, P = 0.05), with mean systolic blood pressure (r = 0.38, P = 0.04), and marginally with total triglycerides (r = 0.34, P = 0.06). These data suggest a relationship between endothelial dysfunction at capillary level and insulin action, as well as providing further evidence for a relationship with other features of the insulin resistance syndrome.

HYPOTHESIS

Endothelial dysfunction precedes the development of both the insulin resistance syndrome and atherosclerosis. Peripheral endothelial dysfunction, at the arteriolar and capillary levels, arises through a complex interplay of genetic and environmental factors and leads to a multifaceted metabolic disturbance comprising insulin resistance and the other features of insulin resistance syndrome (Fig. 1). Thus, insulin resistance syndrome is a marker for peripheral endothelial dysfunc-

tion. In contrast, "central" large-vessel endothelial dysfunction plays a major role in atherogenesis but has little direct metabolic impact. The coexistence of central and peripheral endothelial dysfunction explains the observed association between atherosclerotic vascular disease and insulin resistance syndrome.

This hypothesis could offer new insights into several clinical observations. First, it may be proposed that not all patients with coronary heart disease have an insulin resistance syndrome phenotype because insulin resistance syndrome is not an obligatory precursor of large-vessel atherogenesis, but rather a marker of peripheral endothelial dysfunction. However, subjects with peripheral endothelial dysfunction, such as those with diabetes or poor skeletal muscle capillarization, will be more likely to generate the insulin resistance syndrome phenotype, which accelerates endothelial dysfunction and atherogenesis in the large vessels. It is recognized, however, that additional local factors such as shear stress and rates of cholesterol deposition are likely to play important roles in restricting plaque formation to specific sites. In summary, we propose that peripheral endothelial dysfunction is the principal cause of insulin resistance and insulin resistance syndrome. How might this hypothesis be tested?

TEMPORAL PRECEDENCE AND EXPERIMENTAL REVERSIBILITY

The most rigorous criteria for causality are temporal precedence and experimental reversibility. Importantly, the chronological relationship of arteriolar and capillary endothelial dysfunction to insulin resistance has not been addressed directly by prospective studies. Recognition of the multifunctional nature of the endothelium, its diverse roles in different vascular beds, and the application of new methods to detect dysfunction in its earliest stages will facilitate the testing of both primacy and reversibility at different sites. Interventions such as nitric oxide donors and antioxidants may be useful tools with which to test reversibility. We suggest that techniques for measuring regional blood flow, such as arteriovenous differences and interstitial concentrations of hormones, metabolites, and endothelial products, will allow endothelial biology in large vessels, arterioles, and different capillary beds to be better characterized. This approach may allow a test of the hypothesis that endothelial dysfunction is the central, unifying abnormality underlying the pathogenesis of insulin resistance and the insulin resistance syndrome and explains the association between insulin resistance and atherosclerotic vascular disease.

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