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The Vascular Endothelium in Diabetes and its Potential as a Therapeutic Target

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In addition to functioning as the innermost barrier separating the blood from tissue interstitium, vascular endothelium actively regulates vessel functions by both secreting vasoactive factors and direct coupling to nearby smooth muscle. As arterial and arteriolar function varies depending on their size and location the role played by the endothelium differs accordingly. The conduit arteries mainly regulate arterial plasticity/compliance, the resistance arterioles blood pressure and total blood flow to tissues, the pre-capillary arterioles tissue perfusion and the capillaries exchanges of nutrients, oxygen and hormones between the plasma and tissue interstitium.

Vascular endothelium has long been known to be insulin responsive. Endothelial cells express abundant insulin, insulin-like growth factor I (IGF-I) and the hybrid insulin/IGF-I receptors (1–3). At physiological concentrations, insulin binds and activates the insulin receptors exclusively. It exerts its biological actions mainly via two signaling pathways. One proceeds by activation of phosphatidylinositol 3-kinase (PI-3 kinase)/protein kinase B (PKB or Akt) pathway that leads to the phosphorylation of serine 1176 of the endothelial nitric oxide (NO) synthase (eNOS) to increase NO production (4; 5). NO is a potent vasodilator with important anti-atherosclerotic actions as well. Insulin also signals through the mitogen-activated protein kinase (MAPK) pathway to regulate cell proliferation and production of both the vasoconstrictor endothelin-1 and adhesion molecules (6–9). In the insulin sensitive state, insulin fine-tunes vascular functions via balancing its signals through these two signaling pathways to maintain endothelial health, arterial wall compliance, vascular tone and tissue perfusion.

Diabetes causes significant morbidity and mortality to patients by accelerating atherosclerosis in large and medium arteries and injuring the microvasculature thus precipitating classical retinal, renal and neural complications. Mounting evidence has confirmed the central role of endothelial dysfunction, characterized by abnormal vascular reactivity, increased production of reactive oxygen species, decreased NO bioavailability, and altered barrier function, in the pathogenesis of both macro- and microvascular complications of diabetes. This is not surprising as diabetes is associated with a wide variety of metabolic/biochemical disturbances in many tissues and blood vessels play indispensable role in maintaining tissue function by delivering nutrients, oxygen and hormones and removing metabolic products. Thus, the endothelium is exposed to both environmental and endogenous stimuli such as nutrients, cytokines, chemokines, hypoxia and other factors.

Endothelial dysfunction and endothelial insulin resistance co-exist in the state of insulin resistance including metabolic syndrome, obesity and diabetes. Almost all factors that cause

metabolic insulin resistance also induce endothelial dysfunction and vascular insulin resistance. The term “vascular insulin resistance” can be misleading in that within endothelial cells resistance to insulin action is pathway selective (10–12). While insulin responses through the PI3-kinase/Akt/eNOS pathway are attenuated, its action via the MAPK pathway remains intact or even enhanced in the insulin resistant state. As a result, the net effect of insulin acting on the vasculature is increased production of adhesion molecules and ET-1 and decreased production/bioavailability of NO, tilting the balance towards pro-atherogenic and vasoconstrictive responses (11; 13–15). Markedly increased insulin concentrations which can accompany metabolic insulin resistance may contribute to this process by activating the IGF-I and/or insulin/IGF-I hybrid receptors. Combined, pathway selective insulin resistance and hyperinsulinemia-driven MAPK signaling could handily explain why patients with diabetes have accelerated atherosclerosis and are prone to hypertension and tissue hypoxia (Figure). However, evidence supporting this selective insulin resistance mainly stemmed from in vitro cell culture studies and ex vivo studies using isolated blood vessels. Convincing in vivo evidence remains scant.

The effects of insulin on the microvasculature have garnered much attention over the past decade. For insulin to exert its metabolic actions it has to be first delivered to tissue interstitium after it is secreted by the pancreatic β -cells. Vascular endothelium clearly plays a barrier role and actively with continuous endothelium like muscle, brain and adipose tissue. In the case of skeletal muscle, it is the muscle interstitial insulin concentrations, not the plasma insulin concentrations, that correlate closely with insulin’s metabolic action (16). Evidence from human, animal and cultured cell studies have repeatedly demonstrated that insulin itself actively regulates its own delivery to muscle interstitium by dilating resistance vessels to increase total blood flow, relaxing pre-capillary arterioles to recruit microvasculature and increase endothelial exchange surface area (microvascular recruitment), and trans-endothelial transport of insulin from the plasma compartment to tissue interstitium (17; 18). When infused acutely, insulin increases muscle microvascular perfusion within 5–10 minutes and this action precedes and contributes (up to 40%) to insulin-stimulated glucose uptake in skeletal muscle (19; 20). This action is reduced in the presence of metabolic insulin resistance as seen in obese humans, healthy humans given lipid infusions to raise plasma free fatty acid levels as well as in animal models of insulin resistance (21–23).

Overall, studies from the past two decades have convincingly shown that vascular endothelium is an insulin target and that vascular endothelial dysfunction and vascular insulin resistance play central roles in the pathogenesis of metabolic insulin resistance, organ damage/failure and cardiovascular complications of diabetes. These aggregate findings point to vascular endothelium as a very promising therapeutic target in the prevention and/or management of diabetes and insulin resistance. Reduced endothelial insulin resistance and improved endothelial function in the conduit arteries may reduce macrovascular atherosclerotic complications. In resistance arterioles it could improve blood pressure control. While in the microvasculature it could reduce/prevent microvascular complications and enhance tissue insulin action thus metabolic control.

Currently available glycemic therapies, particularly exercise and insulin sensitization, have shown some salutary effects on endothelial function in patients with diabetes. However, only metformin has demonstrated a positive effect in reducing the clinical macrovascular endpoints in obese patients with T2DM (24). None of these therapeutic modalities target specifically the endothelium and the improved endothelial function associated with these therapies is likely secondary to improved glycemic control and perhaps some direct action on the endothelium. Several lines of evidence have shown that factors that in clinical studies improve insulin sensitivity and glycemic control, such as exercise, angiotensin II type 1

receptor blocker, and glucagon-like peptide 1, are able to increase microvascular recruitment and muscle delivery/action of insulin in experimental animals (25–27). Whether these effects remain in insulin resistant humans are under investigation. More studies are needed to better understand the mechanisms underlying endothelial insulin resistance and endothelial dysfunction in diabetes and other states of insulin resistance and their exact molecular and cellular roles in the pathogenesis of metabolic insulin resistance and diabetic vascular complications. Undoubtedly this will drive the development of endothelium targeted therapies for prevention of diabetes and the vascular injuries that accompany it and other insulin resistant states.

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Figure 1.