Hypertension in Diabetes: The Role of the Vasculature

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Introduction
Arterial hypertension is more common in those with diabetes mellitus (DM) than in the general population [1]. The metabolic syndrome usually precedes type 2 diabetes, in which central adiposity, insulin resistance, and hypertension play central roles. Many surveys have shown a positive correlation between blood pressure and plasma glucose level [1]. Reduction in blood pressure has been shown to occur with better glucose control in diabetic subjects, despite increases in plasma volume and exchangeable sodium [2]. A complex interplay among elevated glucose, insulin, and insulin resistance that favors the evolution of high blood pressure takes place in the vasculature with diabetes.

Role of Endothelial Cells in Hypertension with Diabetes
Endothelial dysfunction, oxidative stress, and inflammation play major roles in the pathogenesis of hypertension in patients with diabetes. Impaired nitric oxide (NO)-mediated vasorelaxation is very common in patients with obesity/obesity metabolic syndrome and diabetes, and usually precedes the development of clinical diabetes [3].

Decreased endothelial-dependent vasorelaxation in obesity and diabetes
Insulin induces vasodilation that depends on NO release [4]. NO synthase inhibition blunts the insulin-mediated increase in skeletal muscle blood flow and causes concomitant hypertension and insulin resistance [5]. Insulin stimulates vascular NO production via signaling through either the insulin or the insulin growth factor (IGF)-1 receptor [4], or through activation of the phosphatidylinositol 3 (PI3)-kinase and, downstream, the protein kinase B (Akt) signaling pathways [6]. In lean individuals, these effects of insulin translate into stimulation of muscle blood flow by a vasodilator effect, which facilitates glucose delivery and uptake [7]. NO-dependent vasodilation is impaired in type 2 diabetic subjects due to decreased production of NO and increased inactivation of NO, and also, probably, due to decreased reactivity of vascular smooth muscle cells (VSMC) to NO.

Decreased production of nitric oxide in obesity and diabetes
High glucose levels suppress NO synthase expression in endothelial cells and VSMC, apparently via protein kinase C (PKC)-dependent mechanisms [8]. This effect, however, is variable, and in several systems, high glucose concentration actually stimulates endothelial NO expression and NO release [9]. Therefore, glucose might have a differential, organ/tissue-specific effect on NO synthase.

O-linked glycosylation of signaling peptides involved in insulin-dependent activation of endothelial NO synthase (eNOS) appears to impair NO production and, hence, NO-dependent vasodilator mechanisms in insulin-resistant patients with essential hypertension and also in type II diabetic patients [10].

Tumor necrosis factor (TNF)-α, which is overexpressed in insulin-resistant states, inhibits flow and insulin signaling, leading to NO production in aortic endothelial cells [11]. Impaired effect of insulin on lipid metabolism leads to increased lipolysis and increased release of fatty acids, which suppress NO production and enhance vascular reactivity.

A significant relationship exists between insulin resistance and plasma concentrations of asymmetric dimethylarginine (ADMA), an endogenous, competitive inhibitor of NO synthase [12••]. Glucose impairs the activity of dimethylarginine dimethylaminohydrolase, the enzyme that catalyzes the breakdown of ADMA and causes ADMA accumulation in rats. The plasma level of ADMA is significantly increased in hypertension and diabetes [12••]. ADMA levels are also higher in patients with impaired renal function due to diminished capacity to excrete ADMA.
Advanced glycosylation end products (AGES) inhibit eNOS activity, in association with a decrease in serine phosphorylation of this enzyme [13].

Increased consumption/destruction of nitric oxide in diabetes

Effects of glucose

Hyperglycemia reduces the availability of NO, in large part owing to increased oxidative destruction of this molecule. Under hyperglycemia, there is increased production of reactive oxygen species (ROS), especially superoxide [3], apparently as a consequence of mitochondrial overproduction, which accompanies hyperglycemia-induced glycolysis in insulin-independent tissues. In diabetes, vitamin C restores impaired endothelial-dependent dilation, suggesting enhanced NO degradation by free radicals [14]. Glycemia-driven increases in production of ROS in mitochondria activate PKC, hexosamine, and polyol pathways, which results in several deleterious consequences, including advanced glycation end products. The pivotal role of glycemia in diabetic endothelial dysfunction is highlighted by observations that improvement in glycemia attained by intensive insulin treatment results in better endothelial function [15].

Role of low-density lipoprotein

In patients with type 2 diabetes, low-density lipoprotein (LDL) cholesterol, which is often oxidized and glycated, inhibits endothelial-dependent vasorelaxation [16]. In a vicious cycle, native LDL, and particularly oxidatively (minimally) modified LDL, induces oxidative enzymes to further increase O_2^- generation in the endothelium, thus providing additional mechanisms for NO scavenging [17]. In endothelial cells, the expression of one of the receptors for ox-LDL, lectin-like ox-LDL receptor-1 (LOX-1), is increased by hyperglycemia in vitro [18•]. Activation of LOX-1 leads to the generation of reactive oxygen species, a decrease in the release of NO from endothelial cells, and increased expression of endothelin-1 (ET-1), angiotensin II receptors (AT_1Rs), and of cell adhesion molecules [19], all of which directly contribute either to hypertension or to vascular damage. Consistent with these effects are the findings that in uncomplicated type 1 and 2 diabetic patients, lipid-lowering therapy might improve endothelial-derived vasorelaxation, in part by increasing vascular NO production [20]. AGEs can bind to LDL close to the LDL receptor-binding domain, thereby blocking the uptake of AGE-modified LDL. Furthermore, AGEs apparently bind to several different types of the scavenger receptor family—for example, scavenger receptors type A (SRA), CD36, and LOX-1. Binding of AGEs to scavenger receptors is followed by endocytosis and loss of scavenging capacity for ligands, such as oxidized LDL, whereas the association of AGEs to SR-B1, which binds high-density lipoprotein (HDL), impairs reverse cholesterol transport [21].

Role of angiotensin II in promoting oxidative stress and endothelial dysfunction

Overexpression of the renin-angiotensin-aldosterone axis cardiovascular tissue might contribute to reduced endothelial function and compliance in patients with diabetes [22]. First, there is evidence for activation of angiotensin-converting enzyme (ACE) and tissue renin in diabetes [23]. Glucose also upregulates AT_1R expression and augments angiotensin II (Ang II)–induced signaling through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway [23]. Second, Ang II increases vascular oxidative stress [22] by increasing the vascular production of reactive oxygen species, in part through the activation of membrane-bound reduced nicotinamide adenine dinucleotide (NADH) and reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, which are present in endothelial cells, VSMCs, fibroblasts, and phagocytic mononuclear cells. ROS are formed by increased activation of xanthine oxidase, the auto-oxidation of NADH, and the inactivation of superoxide dismutase. The resultant increase in NO degradation or inactivation by ROS, rather than reduced NO production itself, apparently plays the principal part in the impairment of endothelium-dependent vasodilation in diabetes and other vascular diseases characterized by enhanced tissue activation of the renin-angiotensin system. Reaction of oxygen radicals with NO leads to the production of peroxynitrate, a potent oxidant that further contributes to vasoconstriction and vascular injury. Endothelial dysfunction and oxidative stress in diabetes can be abrogated by Ang II-receptor blockers and ACE inhibitors [22].

Activation of lipoygenase enzymes

High glucose increases 12- and 15-lipoxygenase activity in endothelial cells, and lipoxygenase enzymes increase NO consumption [24]. Because Ang II is a potent stimulator of 12/15 lipoxygenase activity and expression, this effect can be driven even further by locally generated Ang II.

In addition to the inhibitory effect of AGES on eNOS activity, both early glycation products and AGES directly quench NO [25].

Nitric Oxide–independent Changes in Endothelial Function in Diabetes

Increased tendency for endothelial cell apoptosis

In diabetes, endothelial cell apoptosis is promoted by several factors, thus leading not only to impaired endothelial-dependent vasodilation and increased likelihood of raised blood pressure but also to structural changes, such as increased adhesion of inflammatory cells and platelets, myointimal proliferation, and plaque formation. Proinsulin, at high concentrations, causes apoptosis in cultured human endothelial cells [23]. High glucose levels promote apoptosis through the effects of nonmetabolizable glucose and inhibit proliferation by PKA- and/or PKC-dependent mechanisms.