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Hypertension Management and Microvascular Insulin Resistance in Diabetes

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Abstract

Type 2 diabetes is in essence a vascular disease and is frequently associated with hypertension, macrovascular events, and microvascular complications. Microvascular dysfunction, including impaired recruitment and capillary rarefaction, has been implicated in the pathogenesis of diabetic complications. Microvascular insulin resistance and renin-angiotensin system upregulation are present in diabetes, and each contributes to the development of hypertension and microvascular dysfunction. In the insulin-sensitive state, insulin increases microvascular perfusion by increasing endothelial nitric oxide production, but this effect is abolished by insulin resistance. Angiotensin II, acting via the type 1 receptors, induces inflammation and oxidative stress, leading to impaired insulin signaling, reduced nitric oxide availability, and vasoconstriction. Conversely, it acts on the type 2 receptors to cause vasodilatation. Because substrate and hormonal exchanges occur in the microvasculature, antihypertensive agents targeted to improve microvascular insulin sensitivity and function may have beneficial effects beyond their capacity to lower blood pressure in patients with diabetes.

Keywords

Diabetes; Hypertension; Microcirculation; Insulin resistance; Capillary recruitment; Renin-angiotensin system

Introduction

Patients with type 2 diabetes tend to develop hypertension, which is a major determinant of cardiovascular morbidity and mortality in this patient population. Many clinical studies, including the United Kingdom Prospective Diabetes Study (UKPDS), have shown that tight

blood pressure control in diabetes patients significantly reduces the risks of macrovascular and microvascular complications. Though the mechanisms underlying the intertwined relationship among diabetes, hypertension, and cardiovascular events remain to be defined, microvascular insulin resistance and dysfunction have been implicated as a major culprit.

The microcirculation encompasses all vessels less than 150 μm in diameter, including arterioles, capillaries, and venules. Its major function is to regulate tissue perfusion to ensure adequate delivery of nutrients, oxygen, and hormones; to provide exchange surface area between the plasma compartment and tissue interstitium; and to regulate hydrostatic pressure and peripheral vessel resistance. Microvascular perfusion is determined by precapillary terminal arterioles. Their opening increases microvascular perfusion and expands exchange surface area (capillary recruitment), whereas their closure leads to the opposite, capillary decruitment [1•]. Many physiological factors regulate microvascular perfusion in vivo (Table 1). Among them, insulin plays an important physiological role. We and others have repeatedly demonstrated a vasodilatory effect of physiological concentrations of insulin in the microcirculation of cardiac and skeletal muscle in both humans and laboratory animals [2–4].

In the state of diabetes, microvascular insulin resistance and dysfunction are present. Strong evidence has confirmed that the renin-angiotensin system (RAS) interacts with insulin to regulate tissue perfusion. Because microvascular perfusion mediates tissue delivery of nutrients, oxygen, and hormones, insulin resistance and dysfunction in the microvasculature may play important roles in the development of diabetes-related macrovascular and microvascular complications. This review focuses on the role of microvascular insulin resistance and dysfunction and RAS effects in the pathogenesis and management of hypertension in type 2 diabetes.

Microvascular Insulin Resistance and Dysfunction in Diabetes

In healthy humans, insulin acts on the vascular endothelium to maintain vascular tone and integrity, and thus adequate tissue perfusion. Insulin activates the insulin receptor substrates (IRS)/phosphatidylinositol 3-kinase (PI3-K)/protein kinase B (PKB or Akt)/endothelial nitric oxide synthase (eNOS) pathway [5], leading to increased nitric oxide (NO) production and the dilation of peripheral resistance arteries and precapillary terminal arterioles, as well as increased total blood flow [6] and muscle microvascular perfusion [2,3,7–9]. The effect on microcirculation is rapid (within 5–10 min) [8], and has been shown to be NO-dependent, as inhibition of eNOS with L-nitro-arginine methyl ester (L-NAME) abolishes insulin-mediated microvascular perfusion [7,8]. In addition to its vasodilator action, insulin also causes vasoconstriction, mainly through the activation of the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) kinase (MEK) pathway and the production of vasoconstrictor endothelin 1 (ET-1). In the insulin-sensitive state, insulin fine-tunes vascular tone and tissue perfusion by balancing its signals through these two signaling pathways (Fig. 1A).

Insulin resistance causes endothelial dysfunction and impairs insulin-mediated increases in total muscle blood flow. In insulin-resistant states, insulin action through the PI3-K/Akt/eNOS pathway is blunted but its signals through the MAPK pathway remain intact or are even enhanced, a phenomenon referred to as *selective insulin resistance* [5,10]. This leads to decreased NO availability and same or enhanced ET-1 production, tilting the balance between ET-1 and NO production and resulting in increased vasoconstriction [11,12].

Microvascular insulin resistance and dysfunction are well established in patients and animal models of obesity, diabetes, or both, involving microvasculature in skin, skeletal muscle, cardiac muscle, retina, and kidneys. Indeed, microvascular dysfunction develops

progressively along with an increase in body adiposity. In obese Zucker rats, an animal model of metabolic syndrome, and Zucker diabetic fatty rats, an animal model of type 2 diabetes, basal skeletal muscle microvascular blood volume is decreased; this decrease is coupled with impaired insulin-mediated glucose disposal and capillary recruitment [13•,14]. In humans, insulin resistance associated with simple obesity blunts insulin-stimulated muscle microvascular perfusion and is correlated with decreased whole body glucose disposal [4]. In patients with type 2 diabetes, ingestion of a mixed meal does not increase cardiac microvascular perfusion; paradoxically, it actually decreases this perfusion [15].

The mechanisms underlying the microvascular insulin resistance and dysfunction are under active investigation. Among many biochemical perturbations seen in diabetes, factors that have been clearly implicated in the pathogenesis of microvascular insulin resistance and dysfunction include chronic inflammation, elevation in plasma free fatty acids (FFAs), and overactivation of the RAS in the cardiovascular system. Each of these factors is capable of causing oxidative stress, inflammation, insulin resistance, and endothelial dysfunction. Tumor necrosis factor- α (TNF- α) impairs insulin signals through the PI3-K pathway via a p38 MAPK-dependent mechanism in cultured endothelial cells [16] and blocks insulin-induced capillary recruitment and glucose disposal in rats [17]. The elevated levels of plasma FFAs in diabetes repeatedly have been shown to induce insulin resistance, inflammation, and endothelial dysfunction. Acute elevation of plasma FFAs via systemic lipid infusion induces oxidative stress, activates the nuclear factor (NF)- κ B pathway, impairs endothelium-dependent vasodilation, blunts insulin-mediated vasodilation and NO production in humans, and abrogates insulin-induced or meal-induced muscle capillary recruitment in rats and humans [2,9,18,19]. In cultured endothelial cells, palmitate inhibits insulin-mediated tyrosine phosphorylation of insulin receptor substrate 1, serine phosphorylation of Akt and eNOS, and NO production while increasing IKK β activity [10,20]. Though there is no definitive evidence linking RAS upregulation to microvascular insulin resistance and dysfunction, RAS inhibition using the angiotensin-converting enzyme (ACE) inhibitor quinapril restores the microvascular action of insulin in Zucker diabetic fatty rats, strongly suggesting that the RAS is involved in the development of microvascular insulin resistance and dysfunction in diabetes [13•]. This conclusion is consistent with many clinical observations of treatments aimed at RAS inhibition that attenuate inflammation, improve insulin sensitivity and endothelial function, and reduce cardiovascular morbidity and mortality in diabetes patients [21].

Microvascular insulin resistance and dysfunction are closely related to metabolic insulin resistance in diabetes [1••,5,10]. Insulin-mediated capillary recruitment clearly precedes insulin-stimulated glucose uptake in skeletal muscle [8], and blockade of insulin-mediated capillary recruitment with L-NAME decreases insulin-stimulated glucose disposal by about 40% [7,8]. This finding is not surprising, because in order for insulin to exert its metabolic actions, it first must be delivered to tissue interstitium. Insulin has been shown to regulate its own delivery to muscle interstitium by acting at three discrete steps: dilation of the resistance vessels to increase total blood flow, relaxation of precapillary arterioles to increase microvascular perfusion and exchange surface area (microvascular recruitment), and transendothelial transport of insulin from the plasma compartment to interstitium [1••]. It appears that in the insulin-resistant states, insulin actions at all three steps are impaired [1••].

In addition to functional abnormalities, patients with obesity and diabetes also have structural abnormalities in the microcirculation, including increased wall-to-lumen ratio of the precapillary resistance vessels and reduced number of capillaries within various tissues, a phenomenon termed *capillary rarefaction*. A decrease in capillary density leads to increased diffusion distances and decreased tissue supply of nutrients, hormones, and

oxygen. Together, these abnormalities lead to impaired tissue perfusion, which may be involved in target-organ damage. Indeed, the overall Framingham risk scores inversely correlate with skin capillary recruitment, skin capillary density, and coronary flow reserve.

Microcirculation and Hypertension in Diabetes

Patients with diabetes tend to develop hypertension, which is an independent risk factor for cardiovascular events and contributes significantly to morbidity and mortality in patients with diabetes. Though the exact mechanisms underlying this propensity remain to be clarified, microvascular insulin resistance and dysfunction and microvascular structural abnormalities, together with renal damage, may play major roles.

Microvascular insulin resistance and dysfunction not only decrease tissue perfusion and increase the risks of end-organ damage; they also contribute to the development of hypertension in the presence of insulin resistance. Skin capillary recruitment is inversely correlated with 24-hour systolic blood pressure in obese women [22]. With insulin resistance, endothelium-dependent vasodilation (i.e., NO production) is impaired while the vasoconstrictive signals via the MAPK pathway (ie, ET-1 production) remain intact, leading to decreased vasodilation and enhanced vasoconstriction. The upregulation of the RAS in the vasculature also leads to increased vasoconstriction. Together with the structural abnormalities in the microcirculation, such as increased resistance vessel wall-to-lumen ratio and capillary rarefaction, these changes increase the total peripheral vascular resistance and thus contribute to the development of hypertension.

Hypertension per se is also associated with microvascular dysfunction and insulin resistance. Elevated blood pressure further increases arteriole wall-to-lumen ratio and capillary rarefaction. In hypertensive patients, endothelium-dependent vascular relaxation is clearly impaired [23], and forearm skin microvascular hyperemic response to acetylcholine is decreased [24]. Thus, there is a vicious cycle present in the microcirculation in patients with diabetes, which may partially explain the clinical observations that patients with diabetes have a much greater tendency to develop intractable hypertension and have more frequent and severe end-organ damage. Treatment aimed at disrupting this vicious cycle may help to reduce the prevalence and severity of diabetic complications.

Angiotensin Type 1 Receptor Activity and Microvascular Insulin Sensitivity and Function

In addition to its pivotal role in the regulation of fluid and electrolyte balance and arterial pressure, the RAS also has a major role in modulating vascular insulin sensitivity and endothelial function. The RAS is present both systemically and locally in many tissues, including the cardiovascular system [25,26]. The major biologically active end-product of the RAS is angiotensin (Ang) II, which acts on both angiotensin type 1 receptors (AT₁Rs) and type 2 receptors (AT₂Rs) [25,27]. The AT₁R mediates the vast majority of the cardiovascular, renal, and adrenal actions of Ang II, resulting in arterial vasoconstriction, aldosterone secretion, dipsogenic responses, sympathetic nervous system stimulation, and renal sodium reabsorption. We have recently reported that intravenous injection of losartan, an AT₁R antagonist, acutely increases muscle microvascular perfusion and glucose use, suggesting that basal AT₁R activity restricts muscle microvascular perfusion and reduces substrate delivery to muscle [28•]. It is through this receptor that RAS cross-talks with the insulin signaling pathways [21].

The AT₁R effects directly counter the vasodilatory effect of insulin. Ang II increases ET-1 production and promotes vasoconstriction. It activates the NAD(P)H oxidase and increases

the production of superoxide, which converts NO to peroxynitrite and reduces NO bioavailability [29]. Ang II also directly impairs insulin signaling [30]. In cultured vascular smooth muscle cells and endothelial cells, Ang II increases serine phosphorylation of insulin receptor β -subunit and insulin receptor substrate 1, inhibits PI3-K activity, and reduces endothelial NO production via the AT₁Rs [31,32].

The cardiovascular RAS is upregulated in diabetes, a state that has been implicated in the development of many diabetic cardiovascular complications [21,25,29]. Hyperglycemia increases transcription of angiotensinogen and Ang II production from the local ACE, whereas a high-fructose diet upregulates the AT₁Rs. Conversely, AT₁R blockade with losartan normalizes blood pressure, NAD(P)H oxidase activity, endothelial function, and Ang II-induced vasoconstriction in fructose-fed rats [33]. The enhanced AT₁R effects are particularly important in patients with pre-existing insulin resistance, as insulin resistance and RAS activation aggravate each other and facilitate vasoconstriction by reducing NO bioavailability and enhancing ET-1 production (Fig. 1B). These findings provide an excellent explanation for the clinical observations that RAS inhibition improves endothelial dysfunction, slows the progression of microalbuminuria (which reflects endothelial dysfunction) and of early renal damage from diabetes, and reduces cardiovascular morbidity and mortality in patients with diabetes [21].

Angiotensin Type 2 Receptor Activity and Microvascular Insulin Sensitivity and Function

AT₂R is G-protein-coupled (through G α), and its stimulation is accompanied by an increase in phosphotyrosine phosphatase activity and an inhibition of p44/p42 MAPK. The AT₂R mediates many effects that oppose the actions of Ang II through the AT₁R. The AT₂R has a clearly established vasodilatory function; most studies implicate the bradykinin-NO-cGMP signaling cascade in its vasorelaxant action, as the AT₂R antagonist PD123319, the bradykinin-B₂ receptor (B₂R) antagonist icatibant, and the NOS inhibitor L-NAME all independently block this action [27]. The vasodilator action of the AT₂R is easier to detect during conditions in which the RAS is upregulated, such as sodium restriction, Ang II infusion, or renal vascular hypertension. Strong evidence has confirmed the vasodilatory role of AT₂R in both resistance microvessels and large capacitance vessels such as rat uterine artery, mesenteric arterial segments, and thoracic aorta [27]. In isolated porcine coronary arterioles, higher concentrations of Ang II cause vasodilation, which is eliminated by the AT₂R antagonist PD123319 [34]. In rat heart, chronic candesartan-induced coronary vasodilation is also preventable with L-NAME or PD123319 treatment [35]. In isolated human coronary microarteries, AT₁R blockade prevents Ang II-induced contraction, whereas AT₂R blockade potentiates it; the latter effect can be mimicked by icatibant, L-NAME, or removal of the endothelium [36]. AT₂R also has potent tonic effect on skeletal muscle capillary recruitment. We have recently reported that acute blockade of the AT₂R with PD123319 decreases basal microvascular blood volume by about 80%, a decrease associated with significantly decreased muscle glucose extraction [28•]. Whether this decrease in microvascular blood volume is associated with reduced insulin delivery and action in muscle remains to be determined.

These studies confirm that AT₂R mediates vasodilatory responses in the microcirculation via the bradykinin-NO-cGMP signaling pathway. In addition to the vasodilatory effect, the AT₂R appears to be cardioprotective by inhibiting detrimental cardiac remodeling and improving cardiac systolic and diastolic function after myocardial infarction, and by preventing coronary perivascular fibrosis in response to increased circulating Ang II [27,37].

Management of Hypertension in Diabetes: A Microcirculation and RAS Perspective

Ample evidence has confirmed that hypertension is a major determinant of cardiovascular complications in patients with diabetes, and tight blood pressure control significantly reduces both the morbidity and mortality associated with diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) showed that tighter blood pressure control (10/5 mm Hg) is associated with relative risk reductions of 24% for any diabetes-related end point, 32% for diabetes-related death, 44% for stroke, and 37% for microvascular disease. However, this benefit is not sustained when between-group differences in blood pressure are lost [38•]. Thus, ongoing blood pressure control is of great importance in reducing the morbidity and mortality associated with diabetes.

Several professional organizations, including the American Diabetes Association, the International Diabetes Federation, and the American Association of Clinical Endocrinologists, have recommended the use of either ACE inhibitors or AT₁R blockers as first-line antihypertensive agents in patients with diabetes, as these two classes of medications have repeatedly been shown to reduce cardiovascular and renal morbidity and mortality in patients with diabetes. The cardiovascular and renal benefits of RAS inhibition in diabetes may have reflected improved microvascular insulin sensitivity and function.

Angiotensin Type 1 Receptor Blockade

Many clinical trials have repeatedly demonstrated the beneficial effects of AT₁R blockers not only in reducing cardiovascular events in patients with diabetes but also in reducing the incidence of new-onset diabetes by 19% to 88% in patients without diabetes [21]. Treatment of mildly hypertensive patients with losartan for 1 year significantly reduces the ratio of the media width to lumen diameter and normalizes acetylcholine-induced, endothelium-dependent vasorelaxation in resistance arteries dissected from gluteal subcutaneous biopsies, whereas atenolol induced no change in these parameters despite a comparable degree of blood pressure reduction [39]. Valsartan treatment of patients with essential hypertension for 6 weeks augments the decrease of forearm blood flow in response to intra-arterial infusion of N^G-monomethyl-L-arginine (L-NMMA), independent of blood pressure reduction, suggesting an improved basal NO production and release [40]. Whether the cardiovascular benefits and reduction in diabetes incidence associated with chronic AT₁R blocker treatment are secondary to attenuation of the AT₁R effects alone is not clear. AT₁R blockade leads to increased renin secretion and Ang II production via feedback mechanisms. In addition to stimulating the AT₁Rs, Ang II also potently activates the AT₂Rs, which exert the opposite actions in the vasculature to cause vasodilation [25,27]. Thus, blockade of AT₁Rs could lead to heightened and unopposed activation of the AT₂Rs, and the clinical benefits in cardiovascular events and diabetes prevention observed with AT₁R blockers may very likely be secondary to the combined effects of AT₁R blockade and AT₂R activation. Indeed, our recent observations that acute blockade of the AT₁Rs with losartan dramatically increases basal microvascular recruitment and glucose use in skeletal muscle and that these effects are completely abolished by AT₂R blockade with PD123319 or NOS inhibition with L-NAME [28•] strongly support this possibility. AT₁R blockade thus could lead to decreased cardiovascular morbidity and mortality and improved insulin sensitivity in two ways: 1) by reducing NAD(P)H oxidase activity and oxidative stress to improve insulin sensitivity and endothelial function, and 2) by inducing microvascular vasorelaxation via unopposed AT₂R activity, resulting in increased insulin and substrate delivery to muscle.

ACE Inhibition

Like the AT₁R blockers, ACE inhibitors have also been shown to decrease cardiovascular events in patients with diabetes and to lower the incidence of new diabetes by 14% to 34% in patients with or without hypertension [21]. In the Heart Outcomes Prevention Evaluation (HOPE) extension study, these benefits are maintained for more than 2 years after the study completion [41]. Though the Swedish Trial in Old Patients with Hypertension-2 (STOP-Hypertension-2 study) [42] and the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial [43] did not significantly reduce the incidence of diabetes, the DREAM study did show a significantly increased regression to normoglycemia with ACE inhibition among patients with impaired glucose tolerance or impaired fasting glucose [43].

It is unclear whether the cardiovascular benefits and reduction in diabetes incidence associated with chronic ACE inhibitor treatment is related to the vascular actions of ACE inhibitors. Treatment of hypertensive patients with ACE inhibitors does improve maximal forearm hyperemic blood flow response to ischemia. Chronic treatment of Zucker diabetic fatty rats with quinapril for 15 weeks did not significantly change basal microvascular blood volume but did restore insulin response in muscle capillary recruitment and improve insulin-mediated glucose disposal [13•]. Thus it appears that ACE inhibition does not alter basal microvascular perfusion, as seen with AT₁R blockade, probably because of decreased Ang II stimulation of the AT₂Rs with ACE inhibition. On the other hand, ACE not only hydrolyses biologically inactive Ang I into biologically active Ang II but also acts as a kinin-degrading enzyme and inactivates bradykinin, which causes vasodilation via stimulation of NO and cGMP production and release of prostaglandin E₂ and prostacyclin. Thus, the net vasomotion effect of ACE is vasoconstriction. As ACE inhibition reduces Ang II production, decreases not only AT₁R but also AT₂R stimulation, and increases the concentrations of bradykinin, the effect of ACE inhibition on basal tissue microcirculation should be vasodilatory or neutral.

Dual RAS Blockade

As both ACE inhibition and AT₁R blockade appear to lower blood pressure and decrease cardiovascular events but neither completely inhibits the RAS, many physicians have proposed using an ACE inhibitor in combination with an AT₁R blocker—the so-called dual RAS blockade approach—to avoid the “escape phenomenon” (incomplete suppression of Ang II) with ACE inhibitor monotherapy. This approach appears particularly attractive in patients with diabetes due to the upregulation of RAS in the cardiovascular system. Indeed, in the Candesartan and Lisinopril Microalbuminuria (CALM) trial, a combination of candesartan and lisinopril led to a greater reduction in blood pressure and urinary microalbumin than either agent alone in patients with diabetes [44]. However, the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) showed that dual RAS blockade was no more beneficial than monotherapy with either an ACE inhibitor or an AT₁R blocker in preventing serious outcomes in patients with known vascular disease or diabetes with end-organ damage [45].

The lack of superiority in combination therapy in ONTARGET is not surprising from a microcirculation perspective. As described above, Ang II causes vasoconstriction via the AT₁Rs and vasodilation through the AT₂Rs. Thus selective AT₁R blockade in the presence of upregulated cardiovascular RAS may actually enhance the effect of Ang II on AT₂Rs. On the other hand, ACE inhibition reduces Ang II production, thus reducing its effect on both AT₁Rs and AT₂Rs. However, it does facilitate vasodilation via the bradykinin pathway. Thus, from the microcirculation perspective, the dual blockade approach should be no more beneficial than a monotherapy approach using either class of agents. Given the increased

risk of renal insufficiency, hyperkalemia, and hypotension seen in clinical trials using dual RAS inhibition, more studies are needed before this approach can be recommended as standard therapy.

Direct Renin Inhibition

Increased plasma renin release and activity are associated with many classes of antihypertensive agents, such as AT₁R blockers, ACE inhibitors, calcium channel blockers, and diuretics, because of decreased feedback inhibition, decreased intravascular blood volume, or both. Renin cleaves angiotensinogen to form Ang I, which is the first and rate-limiting step of the RAS cascade. Ang I is further hydrolyzed into biologically active Ang II by ACE. Thus, direct renin inhibition leads to decreased Ang II production and less stimulation on both the AT₁Rs and AT₂Rs. When added to other medications, renin inhibitors could block the feedback increase in renin release and activity, leading to better blood pressure control.

Aliskiren, the only selective renin inhibitor available for clinical use, may have cardiorenoprotective effects in patients with diabetes [46]. It attenuates cardiac and renal damage in transgenic rodents carrying human renin and angiotensin genes and in streptozotocin diabetic rats [47]. Whether these potential benefits are related to increased tissue perfusion remains to be explored. So far, there is a lack of concrete evidence that renin inhibition alters muscle microvascular blood flow. However, renin inhibitors do regulate renal perfusion. When used either alone or in combination with other RAS inhibitors, direct renin inhibition clearly increases renal plasma flow, reduces albuminuria, and improves cardiovascular parameters such as total peripheral resistance, arterial pressure, and left ventricular mass index [48]. In healthy volunteers, renin inhibitors increase renal blood flow by nearly 70% more than ACE inhibitors [49]. As renin inhibition reduces the effect of Ang II on both AT₁Rs and AT₂Rs, and there is no evidence suggesting that it affects the kallikrein system, it is likely that if renin inhibitors do alter tissue microvascular perfusion, they exert vasomotor effects via mechanisms distinct from those of ACE inhibitors or AT₁R blockers. Indeed, renin and prorenin have been shown to exert direct, angiotensin-independent effects via their own receptors [50].

Conclusions

Type 2 diabetes is frequently associated with hypertension, which contributes significantly to the cardiovascular morbidity and mortality in diabetic patients. Microvascular insulin resistance and dysfunction have been implicated as one of the major underlying mechanisms. Patients with diabetes have cardiovascular insulin resistance and RAS activation, both of which can cause microvascular dysfunction. Insulin increases microvascular perfusion by increasing endothelial NO production in the insulin-sensitive state, but this effect is abolished in the presence of insulin resistance. Ang II may either increase or decrease microvascular perfusion, depending on its relative actions on AT₁Rs and AT₂Rs. It decreases microvascular perfusion via the AT₁Rs by inducing inflammation and oxidative stress, leading to impaired insulin signaling, reduced NO availability, and vasoconstriction. Conversely, it acts on the AT₂Rs to cause vasodilation via a bradykinin-NO-dependent mechanism.

The importance of increasing tissue microvascular flow in diabetes cannot be overemphasized. Substrate extraction takes place in the microcirculation, as shown by the formula for the rate of substrate extraction (e):

$$([V] - [A]) = ([I] - [A]) \times (1 - e^{-PS/Q})$$

where V is the venous plasma concentration; I, the interstitial concentration; A, the arterial plasma concentration; P, surface permeability; S, surface area; and Q, the plasma flow rate. Thus, a relatively small increase or decrease in the microvascular surface area could markedly increase or decrease substrate extraction by a given tissue. Such changes may be particularly important in settings where the total flow is limited (for example, with fixed stenosis in major conduit arteries, as seen in coronary artery disease or peripheral vascular disease). Thus, antihypertensive agents targeted to improve microvascular function may have beneficial effects beyond their capacity to lower blood pressure in patients with diabetes. This goal could be achieved by insulin sensitization through pharmaceuticals or lifestyle alteration; by blockade of the AT₁Rs (AT₁R blockers); by decreases in AT₁R stimulation and increases in bradykinin availability (ACE inhibitors); by selective AT₂R stimulation (to be developed and tested); or by a combination of two or more of these methods.

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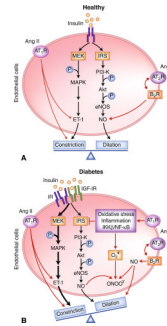


Fig. 1.

Cross-talk between the renin-angiotensin system and insulin affects the microcirculation differently in **A)** health and **B)** diabetes. Akt—protein kinase B; Ang II—angiotensin II; AT₁R—angiotensin type 1 receptor; AT₂R—angiotensin type 2 receptor; B₂R—bradykinin-B2 receptor; eNOS—endothelial nitric oxide synthase; ET-1—endothelin 1; IKK β —inhibitor of κ B kinase β ; IGF-IR—insulin-like growth factor I receptor; IR—insulin receptor; IRS—insulin receptor substrates; MAPK—mitogen-activated protein kinase; MEK—mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; NF- κ B—nuclear factor κ B; P—phosphate; O₂⁻—superoxide anion; ONOO⁻—peroxynitrite; NO—nitric oxide; PI3-K—phosphatidylinositol 3-kinase

Table 1

Factors regulating microcirculation

Factors increasing microvascular perfusion

Angiotensin II
Angiotensin-converting enzyme inhibitors
Angiotensin type 1 receptor blockers
Bradykinin
Endothelium-derived hyperpolarizing factors
Insulin
Exercise
Mixed meal
Renin inhibitors?

Factors causing insulin resistance and dysfunction in microcirculation

Angiotensin II
Aldosterone?
Diabetes
Endothelin 1
Free fatty acids
Hypertension
Inflammatory cytokines
Obesity
