

# Insulin and Endothelial Function: A Brief Review

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## ABSTRACT

**Background:** In recent years, the novel effects of insulin beyond control of glucose metabolism have been appreciated, especially those that impact vascular function. A better understanding of insulin's protective interactions with the endothelium has provided clinicians with a justification for more aggressive use of insulin—not only to control glucose levels, but also to potentially reduce the progression of atherosclerosis and its pathogenic sequelae.

**Objective:** In this brief review, we provide a snapshot of the available research and clinical findings signifying beneficial effects of insulin on the endothelium.

**Methods:** We conducted a MEDLINE search of articles published in English from 1965 through 2007 using the search terms *insulin*, *endothelium*, and *anti-inflammatory*. Articles with a focus on “insulin resistance” per se were excluded from this review.

**Results:** The literature search identified 200 articles that addressed the effects of insulin on endothelium and the interaction between insulin and the vasculature.

**Conclusions:** In addition to mitigating hyperglycemic toxicity, insulin has multiple beneficial interactions with the endothelium in physiologic and disease states. The anti-inflammatory actions of insulin confer beneficial effects in preventing and minimizing morbidity and mortality due to atherosclerosis, especially in acute settings like myocardial infarction. (*Insulin*. 2008;3:185–188) © 2008 Excerpta Medica Inc.

**Key words:** insulin, endothelium, anti-inflammatory, morbidity, mortality.

## INTRODUCTION

Since its discovery, insulin has maintained a key position for its principal effects on glucose metabolism. Within the past several decades, we have witnessed a major surge in our ability to decipher insulin's actions beyond glucose metabolism. One of the key effects of insulin in the vasculature has been its interaction with the endothelium; epidemiologic evidence indicates a potential link between insulin and cardiovascular morbidity and mortality. The prevailing dogma holds that insulin and the endothelium maintain a delicate relationship that is essential for normal functioning of the organ lining the blood vessels of the body. Dysfunction of the endothelium is observed in insulin-resistant states, including obesity, glucose intolerance, and type 2 diabetes mellitus (DM). Insulin resistance and endothelial dysfunction are also frequently accompanied by components of the cardiometabolic syndrome, which layers hypertension, visceral adiposity, and dyslipidemias on abnormalities related to glucose metabolism, contributing to the risk of atherosclerosis and coronary artery disease. This article briefly reviews the interaction between insulin and the endothelium and some of the beneficial effects that insulin confers on endothelial function.

## METHODS

We conducted a MEDLINE search of articles published in English from 1965 through 2007 using the search terms *insu-*

*lin*, *endothelium*, and *anti-inflammatory*. Articles with a focus on “insulin resistance” per se were excluded from this review.

## RESULTS

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### Effects of Insulin on Endothelium at the Molecular and Cellular Level

The healthy endothelium, the largest endocrine organ in the body, is not simply a monolayer of inert cells providing a lining for the lumen of all blood vessels. The endothelium is a dynamic tissue layer that actively responds to physical rheologic influences as well as chemical and hormonal signals through production of multiple factors that regulate vascular tone and permeability, cellular adhesion, thromboresistance, smooth muscle cell proliferation, and vessel wall inflammation.<sup>1</sup> The balance among these factors facilitates endovascular homeostasis. Endothelial dysfunction, as a complex array of associated changes in cellular function, disrupts this balance, predisposing the vessel wall to vasoconstriction, leukocyte adherence, platelet activation, mitogenesis, pro-oxidation, thrombosis, impaired coagulation, vascular inflammation, and atherosclerosis.

Insulin exerts vasodilator and mitogenic effects on the endothelium via 2 distinct pathways.<sup>2</sup> These effects are initiated by the binding of insulin to its cell surface receptor, a ligand-activated tyrosine kinase (**Figure**). Activated insulin receptors phosphorylate intracellular substrates and downstream signaling pathways. The vasodilator and endothelial protective actions of insulin are mediated by phosphatidylinositol 3-kinase (PI 3-kinase)-dependent insulin-signaling pathways in the endothelium leading to the production of nitric oxide (NO). Mitogen-activated protein-kinase-activated insulin-signaling pathways regulate secretion of the vasoconstrictor endothelin-I as well as the mitogenic and growth effects of insulin. The vascular actions of insulin contribute to the coupling of metabolic and hemodynamic homeostasis that occur under healthy conditions.<sup>3</sup>

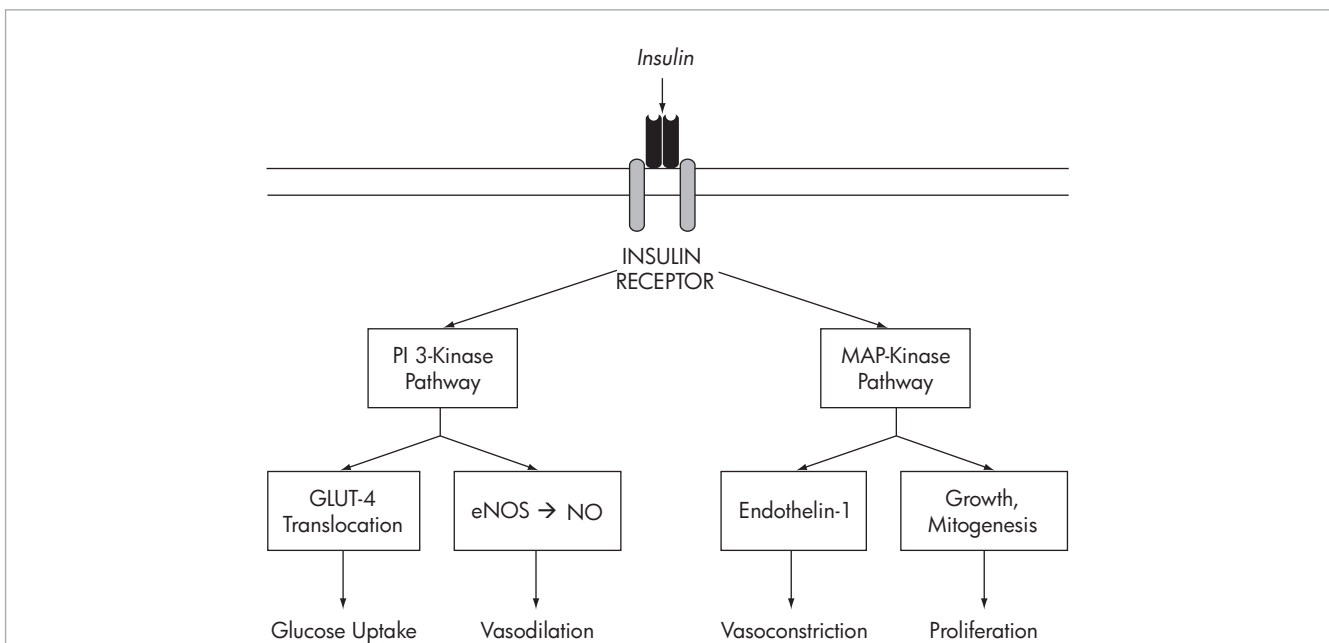
**Insulin-Stimulated Production of Nitric Oxide**

The pioneering experiments of Furchgott and Zawadzki<sup>4</sup> first demonstrated an endothelium-derived relaxing factor that was subsequently found to be NO. Since then, NO has become the most extensively documented endothelium-derived relaxing factor, with a pivotal role in the maintenance of vascular tone and reactivity.<sup>5</sup> Numerous experiments, both in vitro and in vivo, have shown a beneficial effect of insulin on NO bioavailability in the endothelium. Classic endothelial NO production involves calcium-dependent mechanisms used by G-protein-coupled receptors that are, in turn, influenced by calcium-independent effects of the insulin-signaling pathways. Downstream from the insulin receptor, tyrosine phosphorylation of insulin receptor

substrate-I leads to activation of PI 3-kinase and another kinase known as *Akt*. Akt directly phosphorylates and activates the catalytic activity of endothelial NO synthase (eNOS) activity and nitrous oxide production. Other post-translational modifications are also important in the activation of eNOS activity, contributing to regulation of basal and insulin-stimulated production of NO.<sup>6</sup>

At physiologic concentrations, insulin induces a 2-fold increase in resting skeletal muscle blood flow in insulin-sensitive, but not insulin-resistant, human subjects.<sup>3,7</sup> This action of insulin is important for the maintenance of vascular tone as well as the trafficking of various metabolites, signaling hormones and blood gases in and out of the bloodstream in skeletal muscle. Endothelium-derived NO diffuses into adjacent vascular smooth muscle, where it evokes vasorelaxation. This vasorelaxation is well demonstrated in experiments conducted by Baron and Clark<sup>8</sup> in their assessment of insulin-induced leg blood flow in healthy humans. Their experiment showed that 65% of insulin-mediated vasodilation is dependent on intact signaling in the endothelium.

Insulin-mediated vasodilation in skeletal muscle occurs in 2 steps. First, terminal arterioles become dilated, which increases the number of perfused capillaries (capillary recruitment) within a few minutes. Second, relaxation of larger resistance vessels increases overall limb blood flow within 30 minutes after stimulation with physiologic concentrations of insulin. The vasorelaxation and increase in blood flow are closely coupled with the metabolic actions of insulin in skeletal muscle. Augmented blood flow increases the delivery of insulin and metabolites to skeletal muscle,



**Figure.** General features of insulin signal transduction pathways in the endothelium. PI 3 = phosphatidylinositol 3; MAP = mitogen-activated protein; GLUT-4 = glucose transporter-4; eNOS = endothelial nitric oxide synthase; NO = nitric oxide.

where insulin then exerts direct effects at the plasma membrane in the muscle cells to promote glucose uptake via translocation of glucose transporter-4. Increases in insulin-mediated capillary recruitment correlate with enhanced insulin-stimulated glucose uptake in insulin target tissues. In human studies, insulin-induced blood flow has been estimated to account for up to 40% of insulin-mediated glucose uptake.<sup>8</sup> Thus, the vascular actions of insulin have a major impact on promoting glucose metabolism by increasing blood flow with insulin and nutrient delivery to the cellular sites of glucose uptake. These beneficial interactions between insulin and endothelium are also observed in type 2 DM, as shown in a key study by Vehkavaara et al.<sup>9</sup> In this setting, insulin therapy resulted in significant improvement in endothelial-dependent and -independent vasodilation.

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### Anti-Inflammatory Effects of Insulin

Atherosclerosis is an inflammatory state of the vessels associated with endothelial dysfunction. Insulin suppression of this process has been shown in both in vitro and in vivo studies. Using human aortic endothelial cells in culture, insulin reduced the surface protein expression of a proinflammatory intercellular adhesion molecule-1 (ICAM-1), the chemokine monocyte chemoattractant protein-1 (MCP-1), and the key proinflammatory transcription factor, nuclear factor-kappa B (NF- $\kappa$ B), at physiologically relevant concentrations of insulin.<sup>10</sup> This finding was also confirmed in obese subjects, in whom the use of an insulin infusion suppressed reactive oxygen species generation, p47<sup>phox</sup> expression (an activity indicator for nicotinamide adenine dinucleotide phosphate oxidase, an enzyme that generates endothelial superoxide radical), NF- $\kappa$ B binding, and increased inhibitor kappa B- $\alpha$  expression by mononuclear cells.<sup>11</sup>

In addition, insulin causes an acute reduction in plasma concentrations of ICAM-1, MCP-1 and proinflammatory transcription factor, early growth response factor 1, and plasminogen activator inhibitor-1 (PAI-1). Insulin has also been shown to suppress matrix metalloproteinase-9 (MMP-9) and vascular endothelial growth factor, 2 key mediators involved in the spread of inflammation and increases in vascular permeability.<sup>12</sup>

In patients with acute myocardial infarction, insulin infusion resulted in suppression of C-reactive protein (CRP) and serum amyloid A up to 40% within 24 hours of initiation of the insulin infusion while glucose concentrations were not allowed to change.<sup>13</sup> This effect of insulin was also observed

in patients undergoing coronary artery bypass grafting in other studies.<sup>14</sup> Interestingly, these benefits of insulin were observed only when insulin was given intravenously and not subcutaneously.

The cardioprotective effects of insulin also include reduction in infarct size in animals and humans with acute myocardial infarction.<sup>15</sup> This effect appears to be secondary to reduction in CRP levels with intravenous infusion of insulin.<sup>16</sup> Such an effect has been observed in experimental myocardial infarction in both rats and dogs in association with the suppression of proapoptotic factors by insulin. In these models, insulin infused before reperfusion reduced the size of the infarct by 45%.<sup>17</sup> In this context, it is of interest that administration of CRP to rats undergoing experimental myocardial infarction increases the size of the infarct, whereas prior administration of synthetic molecules that bind CRP and thus prevent its action reduces the size of the infarct. Thus, the suppressive action of insulin on CRP may also contribute to a marked reduction in the size of the infarct.

Treatment of acute myocardial infarction with insulin in humans also suppresses PAI-1, pro-MMP-1. In patients who were treated in an intensive-care unit, insulin infusions have been shown to suppress inducible NO synthase expression in the liver and reduce plasma concentrations of nitrite and nitrate, the 2 metabolites of NO.<sup>14</sup>

Insulin also serves to minimize endothelial dysfunction indirectly. Insulin's action on platelets, macrophages, and coagulation factors ultimately results in preservation of endothelial function. The interaction of platelets with collagen under flowing whole-blood conditions mimics the early steps of arterial thrombus formation in vivo. Collagen offers a natural, immobilized ligand for platelets, and high shear rates (>800 s<sup>-1</sup>) provide additional flow-related stimulation of platelets. In a study by Westerbacka et al,<sup>18</sup> insulin at physiologic doses attenuated crucial steps in arterial thrombus formation, including the inhibition of platelet-collagen and subsequent platelet-platelet interactions in healthy subjects, although these benefits of insulin were absent in obese insulin-resistant patients.

### CONCLUSIONS

The fascinating positive effects of insulin on the endothelium have expanded our notion that insulin is simply a hormone that lowers glucose levels. Improvements in insulin action not only improve glucose metabolism but also affect endothelial function as well as the underlying risk for atherosclerosis and cardiovascular complications of diabetes. Further understanding of insulin's vascular actions in health and disease states may provide new insights into how the multiple metabolic and vascular effects of this hormone can improve the clinical outcomes of our patients.

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