Resistance to insulin-stimulated glucose uptake is associated with increased risk for cardiovascular disease [1]. Risk factors for cardiovascular disease tend to cluster within individuals, and insulin resistance may be the link between hypertension and dyslipidemia. Depending on the populations studied and methodologies used for defining insulin resistance, approximately 25% to 40% of nonobese nondiabetic patients with hypertension are insulin-resistant [2]. Insulin resistance also has been observed in genetic and acquired animal models of hypertension. A constellation of insulin resistance, reactive hyperinsulinemia, increased triglycerides, decreased high-density lipoprotein cholesterol, and hypertension was designated as syndrome X by Reaven in 1988 [3].

Although a number of putative mechanisms have been proposed, it is unclear whether insulin resistance or reactive hyperinsulinemia, or both, actually cause hypertension. The recent observations that insulin-sensitizing agents attenuate the development of hypertension lend credence to this hypothesis [4]. As discussed subsequently, however, these agents may lower blood pressure by different mechanisms. Whatever mechanism may be involved, the observation that a single agent may have the capacity to both increase insulin sensitivity and lower blood pressure is potentially of considerable clinical significance.

Non–insulin-dependent diabetes mellitus represents an extreme of insulin resistance. Among diabetics, a two- to threefold increased prevalence of hypertension exists. Hypertension is associated with a fourfold increase in mortality among patients with non–insulin-dependent diabetes, and antihypertensive drug therapy has a beneficial impact on both macrovascular and microvascular disease [5]. Despite the potential concern that diuretics may augment insulin resistance, diabetic patients benefit from antihypertensive therapy with diuretics. The renal protective effect of antihypertensive drugs varies among different classes of agents. Angiotensin-converting enzyme inhibitors decrease proteinuria and retard the progression of renal insufficiency in diabetic patients with normal blood pressure and hypertension.
5.2 Hypertension and the Kidney

This benefit is independent of an effect on blood pressure and may be related specifically to the capacity of these agents to dilate the efferent renal arteriole. Results of studies evaluating the effects of calcium antagonists on the progression of diabetic nephropathy are varied. Some studies suggest that dihydropyridine calcium antagonists accelerate the progression of diabetic nephropathy, particularly in the short term. Additional studies are required to evaluate the antihypertensive potential of insulin-sensitizing agents in patients with non-insulin-dependent diabetes.

---

**FIGURE 5-1**
Hyperlipidemia and hypertension. A, Epidemiologic studies document an association between serum cholesterol and blood pressure in men and women. B, Based on data from the National Health and Nutrition Examination Survey II, persons with hypertension have a high prevalence of hyperlipidemia and vice versa [6]. (Panel A from Bonna and Thelle [7]; with permission.)

**FIGURE 5-2**
Insulin resistance and hypertension. A, Genetic and nutritional factors contribute to insulin resistance and resultant hyperinsulinemia. In addition to obesity and type II diabetes, hyperlipidemia and hypertension also may be associated with insulin resistance. Insulin resistance may account for the association of hyperlipidemia with hypertension. B, Insulin resistance is associated with hypertension in a number of clinical and experimental settings. (Panel A from Ferrari and Weidmann [8]; with permission.)
Insulin Resistance and Hypertension

**FIGURE 5-3**
Insulin resistance based on glucose and insulin responses to glucose load. In response to an oral glucose load of 75 g, compared with persons with normal blood pressure, patients with hypertension tend to have higher plasma glucose and insulin levels. These data suggest that patients with hypertension are insulin resistant.

(From Ferrannini and coworkers [9]; with permission.)

**FIGURE 5-4**
Salt sensitivity. Persons who have salt-sensitive hypertension tend to be more insulin-resistant than are those who are salt-resistant. That is, patients who are salt-sensitive have higher plasma glucose and insulin responses to a glucose load than do those who are salt-resistant.

(From Bigazzi and coworkers [10]; with permission.)

**FIGURE 5-5**
Insulin sensitivity. Insulin sensitivity also may be assessed using the euglycemic insulin clamp technique. The frequency distribution for insulin-mediated glucose disposal during euglycemic insulin clamping (M value) differs in persons with normal blood pressure and those with hypertension. The percentage of persons with hypertension considered insulin-resistant depends on the definition of insulin resistance. In this study, 27% of patients with hypertension were classified as being insulin-resistant based on an M value over two SDs above the mean for persons with normal blood pressure.

(From Lind and coworkers [2]; with permission.)

**FIGURE 5-6**
As originally defined, syndrome X includes hypertension, hyperinsulinemia, increased plasma triglycerides, and decreased HDL cholesterol. The syndrome also may be associated with clustering of additional cardiovascular disease risk factors.

**SYNDROME X AND ASSOCIATED CONDITIONS**

- Hypertension
- Hyperinsulinemia
- Increased triglycerides
- Decreased high-density lipoprotein cholesterol
- Increased low-density lipoprotein cholesterol
- Decreased plasminogen activator
- Increased plasminogen activator inhibitor
- Increased blood viscosity
- Increased uric acid
- Increased fibrinogen (?)
Hypertension and the Kidney

Compensatory hyperinsulinemia

- Obesity
- Nutrition
- Genetic predisposition

Resistance to insulin-stimulated glucose uptake

Obesity

Vascular growth

Increased sympathetic nervous system activity

Hyperglycemia

Hyperlipidemia

Increased α1-adrenergic receptors

Impaired endothelium-dependent vasodilation

Increased sympathetic nervous system activity

Vascular growth

Antinatriuresis

Increased α1-adrenergic receptors

Impaired endothelium-dependent vasodilation

Increased sympathetic nervous system activity

Vascular growth

Antinatriuresis

Increased α1-adrenergic receptors

Impaired endothelium-dependent vasodilation

Hypercholesterolemia (low-density lipoprotein, lipoprotein (a))

Endothelial injury

Increased endothelial superoxide anion production

Increased degradation of nitric oxide

Impaired endothelium-dependent vasodilation

Hypercholesterolemia (low-density lipoprotein, lipoprotein (a))

Endothelial injury

Increased endothelial superoxide anion production

Increased degradation of nitric oxide

Impaired endothelium-dependent vasodilation

Sulfonylureas

Glyburide

Biguanides

Metformin

Thiazolidinediones

Pioglitazone

Sulfonylureas

Glyburide

Biguanides

Metformin

Thiazolidinediones

Pioglitazone

Effects of chemically distinct oral hypoglycemic agents on blood pressure. Sulfonylureas stimulate endogenous insulin secretion and do not lower blood pressure. In contrast, biguanides and thiazolidinediones increase insulin sensitivity without stimulating endogenous insulin secretion, and drugs in these classes lower blood pressure.

Pioglitazone in the treatment of hypertension in rats. A, Systolic blood pressures in Dahl-salt-sensitive rats treated with either vehicle or pioglitazone (a thiazolidinedione) for 3 weeks. Pioglitazone attenuated development of hypertension in this animal model. Weight gain did not differ in the two groups.

(Continued on next page)
**B. HEMODYNAMIC MEASUREMENTS IN DAHL-SALT-SENSITIVE RATS**

<table>
<thead>
<tr>
<th></th>
<th>Mean intra-arterial pressure, mm Hg</th>
<th>Cardiac index, mL/min/100 g</th>
<th>Total peripheral resistance, mm Hg/mL/min/100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>129 ±1</td>
<td>51.4 ±1.6</td>
<td>250 ±0.07</td>
</tr>
<tr>
<td>Group treated with pioglitazone</td>
<td>121 ±3*</td>
<td>59.1 ±1.7*</td>
<td>2.07 ±0.07*</td>
</tr>
</tbody>
</table>

*P<0.05

**FIGURE 5-11** (Continued)

B. Direct intra-arterial pressure and cardiac index (thermodilution) in these same chronically instrumented, conscious pioglitazone-treated and control rats. Compared with control animals, rats treated with pioglitazone had lower mean arterial pressure, higher cardiac index, and lower total peripheral resistance. Thus, attenuation of hypertension by pioglitazone is due to a reduction of peripheral resistance. (From Dubey and coworkers [11]; with permission.)

**AGENTS THAT INCREASE INSULIN SENSITIVITY, DECREASE PLASMA LIPID CONCENTRATIONS, AND LOWER BLOOD PRESSURE IN ANIMAL MODELS AND PRELIMINARY STUDIES IN HUMANS**

<table>
<thead>
<tr>
<th>agent</th>
<th>model</th>
<th>species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneously hypertensive rats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humans (?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vanadyl sulfate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneously hypertensive rats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fructose-fed rats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bromocriptine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneously hypertensive rats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clofibrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dahl-salt-sensitive rats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenfluramine derivatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fructose-fed rats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lovastatin/pravastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dahl-salt-sensitive rats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneously hypertensive rats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human (?)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MODELS IN WHICH THIAZOLIDINEDIONES LOWER BLOOD PRESSURE**

Dahl-S rat
1-Kidney, 1-clip rat
Obese Zucker rat
Fructose-fed rat
L-NNA-treated rat
SHR
Obese rhesus monkey
Watanabe hyperlipidemic rabbit
Obese human

**FIGURE 5-12**

Thiazolidinediones lower blood pressure in several models of experimental hypertension and in obese humans.

**FIGURE 5-13**

Agents that increase insulin sensitivity, decrease plasma lipid concentrations, and lower blood pressure in animal models and preliminary studies in humans.

**EFFECT OF CHOLESTEROL REDUCTION ON BLOOD PRESSURE RESPONSE TO MENTAL STRESS IN PATIENTS WITH NORMAL BLOOD PRESSURE AND HIGH CHOLESTEROL**

<table>
<thead>
<tr>
<th></th>
<th>Systolic blood pressure</th>
<th>Diastolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Stress</td>
</tr>
<tr>
<td>Placebo group</td>
<td>122</td>
<td>141</td>
</tr>
<tr>
<td>Group treated with lovastatin</td>
<td>119</td>
<td>133*</td>
</tr>
</tbody>
</table>

*P<0.05

**FIGURE 5-14**

Clofibrate in prevention of hypertension in rats. Clofibrate prevents the development of hypertension in Dahl salt-sensitive rats. This agent does not affect blood pressure in Dahl salt-resistant rats. (From Roman and coworkers [12]; with permission.)

**FIGURE 5-15**

In humans with normal blood pressure who have high serum cholesterol concentrations, treatment with lovastatin lowers serum cholesterol and attenuates the systolic blood pressure response to mathematics-induced stress. (From Sung and coworkers [13]; with permission.)
5.6 Hypertension and the Kidney

ANTIHYPERTENSIVE MECHANISMS OF INSULIN-SENSITIZING AGENTS

- Block agonist-induced calcium ion entry into vascular smooth muscle cells
- Inhibit agonist-mediated vasoconstriction
- Inhibit growth of vascular smooth muscle cells
- Augment endothelium-dependent vasodilation
- Direct effect
- Metabolic effect
- Natriuresis
- Increase 20-hydroxy-eicosatetraenoic acid production
- Increase renal medullary blood flow

**FIGURE 5-16**
Insulin-sensitizing and lipid-lowering agents may lower blood pressure by a number of different mechanisms. Different agents may act through different mechanisms.

![Graph showing changes in intracellular calcium concentrations](image)

**FIGURE 5-17**
Use of ciglitazone to abolish calcium concentration elevation. Ciglitazone, a thiazolidinedione, abolishes agonist-stimulated sustained elevations of intracellular calcium concentrations. Shown are time-dependent plots of changes in intracellular calcium (in arbitrary units; [Ca^{2+}]_i) induced by platelet-derived growth factor (PDGF) in human glioblastoma cells with and without preincubation with ciglitazone. A, Addition of PDGF to control cells is indicated by the vertical line. B, An identical experiment conducted on cells pretreated with ciglitazone. The capacity of this agent to shorten the duration of agonist-stimulated increases in intracellular calcium may result in attenuation of both growth of vascular smooth muscle cells and vasoconstriction. (From Pershadsingh and coworkers [14]; with permission.)

**FIGURE 5-18**
Use of metformin to attenuate intracellular calcium concentration elevation. Metformin is a biguanide that attenuates agonist-stimulated increases of intracellular calcium concentrations in vascular smooth muscle. (From Bhalla and coworkers [15]; with permission.)
Insulin Resistance and Hypertension

**FIGURE 5-19**
Effect of pioglitazone on insulin-induced proliferation of arterial smooth muscle cells. Inhibition of insulin-stimulated vascular hyperplasia and hypertrophy is one potential mechanism by which insulin-sensitizing and lipid-lowering agents may decrease peripheral resistance. Two kinds of evidence suggest that thiazolidinediones inhibit the growth of vascular smooth muscle cells in vitro. Shown here, pioglitazone inhibits insulin-stimulated proliferation of vascular smooth muscle cells. Pioglitazone also inhibits 3H-thymidine incorporation in vascular smooth muscle cells (Fig. 5-19). FCS—fetal calf serum. (From Dubey and coworkers [11]; with permission.)

**FIGURE 5-20**
Effect of pioglitazone on 3H-thymidine incorporation in vascular smooth muscle cells. 3H-thymidine incorporation is stimulated by insulin, fetal calf serum (FCS), and epidermal growth factor (EGF). Pioglitazone inhibits 3H-thymidine incorporation stimulated by each of these mitogens. Similar observations have been made with pravastatin and lovastatin. (From Dubey and coworkers [11]; with permission.)

**FIGURE 5-21**
Decreases in mean arterial pressure in rats treated with pioglitazone and control Dahl-salt-sensitive rats in response to graded infusions of norepinephrine and angiotensin II. In vivo, pressor responses to norepinephrine and angiotensin II are II attenuated in Dahl-salt-sensitive rats treated with pioglitazone [16]. (From Kotchen and coworkers [16]; with permission.)

**FIGURE 5-22**
Half-maximal values for norepinephrine-induced contraction in aortic strips preincubated with insulin, pioglitazone, or both. In vitro, pressor responsiveness of aortic strips to norepinephrine-induced contraction is inhibited by preincubation with insulin plus pioglitazone [16]. The half-maximal value is increased for strips incubated with insulin plus pioglitazone (ie, higher concentrations of norepinephrine are required to achieve half-maximal contraction) but not in strips incubated with insulin alone or pioglitazone alone.
Impaired endothelium-dependent vascular relaxation and insulin resistance. Insulin resistance is associated with impaired endothelium-dependent vascular relaxation, which is a defect that may be corrected by insulin-sensitizing agents. One approach to evaluating vascular endothelial function is to measure vascular relaxation in response to acetylcholine. EDRF—endothelium derived relaxing factor.

**FIGURE 5-24**
Half-maximal values for acetylcholine-induced vasodilation in aortic strips preincubated with insulin, pioglitazone, or both. In the presence of insulin, pioglitazone augments endothelium-dependent vasodilation. In vitro, the half-maximal values for acetylcholine-induced vasodilation is less in aortic strips incubated with insulin plus pioglitazone (ie, the strips are more responsive to acetylcholine) than in control strips or strips incubated with insulin alone or pioglitazone alone [16].

**FIGURE 5-25**
Effect of clofibrate on 20-hydroxy-eicosatetraenoic (20-HETE) production in Dahl-salt-sensitive rats. Insulin stimulates sodium reabsorption in the proximal tubule. Consequently, lowering plasma insulin concentrations by increasing insulin sensitivity would potentially result in less sodium retention. In addition, clofibrate induces renal P-450 fatty acid w-hydroxylase activity and, hence, increases metabolism of arachidonic acid to 20-HETE. (From Roman and coworkers [12]; with permission.)

**FIGURE 5-26**
20-Hydroxy-eicosatetraenoic acid inhibits chloride transport in the thick ascending limb of the loop of Henle. This inhibition results in a natriuretic effect in the Dahl-salt-sensitive rat. This may be the mechanism by which clofibrate prevents hypertension in this animal model.

**FIGURE 5-27**
Benefits of hypertension control and blood glucose controls are well established in diabetic patients. Noninsulin-dependent diabetes mellitus represents an extreme of insulin resistance, and hypertension is a major contributor to the cardiovascular complications of diabetes. Despite the potential concern that diuretics increase insulin resistance, overall cardiovascular disease morbidity and mortality are reduced in diabetic patients with hypertension by antihypertensive therapy with regimens that include diuretics.
**EFFECT OF ANTIHYPERTENSIVE AGENTS ON INSULIN SENSITIVITY AND RENAL FUNCTION IN DIABETIC PATIENTS**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Insulin sensitivity</th>
<th>Renal protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Increase</td>
<td>+</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Decrease</td>
<td>?</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>Decrease</td>
<td>0</td>
</tr>
<tr>
<td>α1-Blockers</td>
<td>Increase</td>
<td>0</td>
</tr>
<tr>
<td>Calcium ion antagonists</td>
<td>0</td>
<td>-7</td>
</tr>
<tr>
<td>Dihydropyridines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Increase</td>
<td>+?</td>
</tr>
</tbody>
</table>

Different antihypertensive agents have different effects on insulin sensitivity, and in diabetic patients, on renal function. Question mark indicates inconsistent study results; plus sign indicates a protective effect; minus sign indicates no protection.

**FIGURE 5-28**
Course of diabetic nephropathy during effective antihypertensive treatment in patients with overt diabetic nephropathy. Effective antihypertensive therapy with regimens that include diuretics also decreases the rate of progression of renal failure (both the glomerular filtration rate and albumin excretion) in patients with diabetic nephropathy. (From Parving and coworkers [17]; with permission.)

**FIGURE 5-29**
Different antihypertensive agents have different effects on insulin sensitivity, and in diabetic patients, on renal function. Question mark indicates inconsistent study results; plus sign indicates a protective effect; minus sign indicates no protection.

**FIGURE 5-30**
Cumulative incidence of events in patients with diabetic nephropathy in captopril and placebo groups. **A**, Time to doubling of serum creatinine. **B**, Time to end-stage renal disease or death. In type I diabetic patients with nephropathy and either normal blood pressure or hypertension, treatment with angiotensin-converting enzyme inhibitors decreases proteinuria and retards the rate of progression of renal insufficiency. The cumulative incidence of doubling of serum creatinine concentrations over time and development of end-stage renal disease are less in patients treated with captopril than in those treated with placebo. (From Lewis and coworkers [18]; with permission.)
5.10 Hypertension and the Kidney

Changes of Mean Blood Pressure, Proteinuria, and Glomerular Filtration Rate in Treatment with Different Antihypertensive Agents in Patients with Insulin-Dependent Diabetes Mellitus and Non-Insulin-Dependent Diabetes Mellitus Who Have Microalbuminuria or Macroalbuminuria

<table>
<thead>
<tr>
<th>Treatment type</th>
<th>Patients, n</th>
<th>( \Delta \text{MBP}, % )</th>
<th>( \Delta \text{Uprot}, % )</th>
<th>( \Delta \text{GFR}, % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>244</td>
<td>-2</td>
<td>+39</td>
<td>-8</td>
</tr>
<tr>
<td>Conventional (diuretics and ( \beta )-blockers)</td>
<td>213</td>
<td>-10</td>
<td>-20</td>
<td>-9</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>489</td>
<td>-16</td>
<td>-52</td>
<td>-1</td>
</tr>
<tr>
<td>Calcium antagonists:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All except nifedipine and nitrendipine</td>
<td>63</td>
<td>-16</td>
<td>-42</td>
<td>+2</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>63</td>
<td>-12</td>
<td>+2</td>
<td>-48</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>39</td>
<td>-17</td>
<td>-48</td>
<td>+30</td>
</tr>
</tbody>
</table>

**Figure 5-31**

Despite similar control of hypertension, different classes of antihypertensive agents have different effects on renal function in patients with diabetic nephropathy. GFR—glomerular filtration rate; MBP—mean blood pressure; Uprot—urine protein. (From Bretzel [19]; with permission.)

**References**