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 $^{3}$H-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 $^{3}$H-thymidine incorporation in vascular smooth muscle cells. $^{3}$H-thymidine incorporation is stimulated by insulin, fetal calf serum (FCS), and epidermal growth factor (EGF). Pioglitazone inhibits $^{3}$H-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 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.
5.8 Hypertension and the Kidney

**FIGURE 5-23**
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 (i.e., 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-H ETE. (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.

**TABLE 5-2**

<table>
<thead>
<tr>
<th>BENEFITS OF CONTROL OF HYPERTENSION AND DIABETES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Decreased nephropathy</td>
</tr>
<tr>
<td>Decreased retinopathy</td>
</tr>
<tr>
<td>Decreased stroke, myocardial infarction</td>
</tr>
<tr>
<td>Drug specific (?)</td>
</tr>
<tr>
<td>Diabetes (type I)</td>
</tr>
<tr>
<td>Decreased nephropathy</td>
</tr>
<tr>
<td>Decreased retinopathy</td>
</tr>
<tr>
<td>Decreased neuropathy</td>
</tr>
</tbody>
</table>

---

**FIGURE 5-28**

Acetylcholine x 10^{–7} (log M)

Control

Insulin

+ pioglitazone

Insulin

Pioglitazone

Protein, pmol/min/mg

Liver

* P < 0.05

Cortex

Outer medulla

Liver

Clofibrate, n = 12

Control, n = 9

20-Hydroxy-eicosatetraenoic acid

+ Na^+ K^+ Ca^{2+} Mg^{2+}

PLA

PLC

2 K^+

3 Na^+

AA

R

20-HETE

+ K^+

– Cl

BENEFITS OF CONTROL OF HYPERTENSION AND DIABETES

Hypertension

Decreased nephropathy

Decreased retinopathy

Decreased stroke, myocardial infarction

Drug specific (?)

Diabetes (type I)

Decreased nephropathy

Decreased retinopathy

Decreased neuropathy

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Insulin Resistance and Hypertension

**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 1 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>∆MBP, %</th>
<th>∆UProt, %</th>
<th>∆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 β-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**