At least 17 million people in the United States have diabetes mellitus, and another 50 million have hypertension. These chronic diseases increasingly coexist in our aging population. Both diseases are important predisposing factors for the development of cardiovascular disease (CVD) and renal disease, and the coexistence of these risk factors is a very powerful promoter of CVD and renal disease. There is accumulating evidence that the rigorous treatment of hypertension and other risk factors such as dyslipidemia and hyperglycemia considerably lessens the burden of CVD and renal disease in patients with diabetes mellitus. There is considerable evidence that strategies addressing diet and exercise reduce the development of diabetes and are an important component of treatment in persons who have established diabetes. There are also considerable data suggesting that the treatment strategies that interrupt the renin-angiotensin system have special benefits in patients with diabetes and may prevent the development of clinical diabetes in hypertensive patients with impaired glucose tolerance. Data from a recent study indicate that the control of systolic blood pressure, using a diuretic agent as part of antihypertensive therapy, reduces the risk of stroke and other CVD end points. Recent reports indicate that angiotensin receptor–blocking agents decrease the rate of development of proteinuria and diabetic renal disease. These observations will likely have a significant impact on treatment of hypertension in patients with type 2 diabetes mellitus.

The prevalence of diabetes, especially type 2 diabetes mellitus, is rapidly increasing throughout the world.1-3 This disease will soon involve more than 20 million people in the United States and 300 million persons worldwide. In the United States, diabetes is now the leading cause of new blindness, end-stage renal disease (ESRD), and nontraumatic amputations.1,2,4 Diabetes is currently the leading cause of ESRD in African Americans as well as others in the United States.5 This increase in the incidence of ESRD, necessitating dialysis and transplantation, is a tremendous burden on our health care resources as well as on families and individuals affected by this medical problem. Nevertheless, cardiovascular disease (CVD) is the major cause of premature mortality in patients with type 2 diabetes6-10 (Figure 1), and hypertension is a major contributor to the development of CVD and renal disease in these patients.11 Accordingly, the pathophysiology of and therapeutic approaches to hypertension in the patient with diabetes are discussed in this review.

HYPERTENSION IN PATIENTS WITH TYPE 1 DIABETES

Patients with type 1 diabetes currently make up about 6% to 8% of the total diabetes population in the United States.1,3 In contrast to patients with type 2 diabetes, those with type 1 diabetes typically develop renal disease before developing hypertension.5,11-13 However, the development of hypertension accelerates the course of microvascular and macrovascular disease in these patients.11-14 Based on clinical trials, antihypertensive therapy in these patients...
should include an angiotensin-converting enzyme inhibitor.\textsuperscript{11,12} Furthermore, β-blockers should not be used as first-line antihypertensive therapy in patients with type 1 diabetes because of their propensity to promote hypoglycemia and reduce the patient's ability to appropriately perceive and manifest hypoglycemic symptoms, as well as their ability to respond physiologically to hypoglycemia.\textsuperscript{11,12} Other aspects of antihypertensive therapy are similar to that for patients with type 2 diabetes, and this is covered in detail in the following sections.

**HYPERTENSION IN PATIENTS WITH TYPE 2 DIABETES**

The prevalence of hypertension in patients with type 2 diabetes is up to 3 times greater than in age- and sex-matched patients with diabetes.\textsuperscript{5,11,12} Increasing age, obesity, and the onset of renal disease are all factors increasing the likelihood of hypertension in the patients with diabetes.\textsuperscript{5,11,12} Obesity, especially central/visceral obesity, is increasingly an important factor predisposing to the development of diabetes and hypertension.\textsuperscript{5,9,11,14} An increased prevalence of obesity in minority populations contributes to the greater incidence of diabetes and hypertension in these populations.\textsuperscript{5,14}

Persons with hypertension have a high prevalence of insulin resistance\textsuperscript{15} and have a substantially increased risk of developing type 2 diabetes mellitus.\textsuperscript{15,16} Insulin resistance is characterized by reduced ability of insulin to stimulate glucose uptake in insulin-sensitive tissues (especially skeletal muscle tissue)\textsuperscript{15,16} (Figure 2). Skeletal muscle phenotypic characteristics of patients with hypertension that predispose to insulin resistance include:

1. Altered composition of skeletal muscle tissue (less slow-twitch

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**Figure 1.** Seven-year incidence of cardiovascular risk in type 2 diabetes mellitus. CVD indicates cardiovascular disease; MI, myocardial infarction. Adapted from Haffner et al.\textsuperscript{9}

**Figure 2.** Angiotensin II–generated reactive oxygen (O$_2^-$) species and Rho-kinase (ROK) activation in impaired glucose utilization in skeletal muscle. Akt indicates protein kinase C; AT$_1$-R, angiotensin type-1 receptor; GLUT4, glucose transporter 4; IRS, insulin receptor substrate; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; NOS, nitric oxide synthase; ONOO$^-$, peroxynitrite; PH, pleckstrin homology domain; P13-K, phosphatidylinositol-3-kinase. Reprinted with permission from the American Physiological Society.\textsuperscript{20}
muscle and cardiovascular tissue C signaling pathway in skeletal phosphoinositol-3-kinase/protein kinase to decrease signaling through the tissue angiotensin II has been shown sensitive tissue (Figure 2). Increased system in this and other insulin—insulin are related, in part, to the over—delivery of insulin and glucose to skeletal muscle and increased fat interspersed between insulin—sensitive muscle fibers and fat deposition in skeletal muscle.14,16 Both aging and a sedentary lifestyle predisposed to lessening of slow—twitch insulin—sensitive fiber and fat deposition in skeletal muscle.14

Postreceptor abnormalities in metabolic signaling responses to insulin in skeletal muscle tissue (Table 1).11,14,16 Aging and a sedentary lifestyle predisposed to lessening of slow—twitch insulin—sensitive fiber and fat deposition in skeletal muscle.14

Postreceptor abnormalities in metabolic signaling responses to insulin are related, in part, to the overexpression of the renin—angiotensin system in this and other insulin—sensitive tissue (Figure 2). Increased tissue angiotensin II has been shown to decrease signaling through the phosphoinositol—3—kinase/protein kinase C signaling pathway in skeletal muscle17,18 and cardiovascular tissue.11,14,19,20 These observations of interference of angiotensin II with insulin signaling may explain why strategies that interrupt the renin—angiotensin system may lessen the development of type 2 diabetes.21—23 On the one hand, certain antihypertensive agents may increase the propensity for hypertensive patients to develop type 2 diabetes mellitus.15,16 In a large prospective cohort study that included 12 550 adults, hypertensive patients who were taking β—blockers had a 28% higher risk of development of diabetes compared with those taking no antihypertensive medications.15 Potential mechanisms by which β—blockers may increase insulin resistance and the predistribution to hypertension have been reviewed16 and include weight gain and decreased blood flow to skeletal muscle tissues.

HYPERTENSION AND CVD IN TYPE 2 DIABETES

Hypertension markedly increases the risk for CVD in patients with type 2 diabetes.11 Within the Multiple Risk Factor Intervention Trial (MRFIT),9 more than 5000 patients with diabetest were followed for 12 years and compared with more than 350,000 persons without diabetes. The MRFIT confirmed that hypertension, elevated cholesterol level, and cigarette use were independent CVD risk factors in men with diabetes and that their presence had a greater impact on CVD risk in men with diabetes compared with those without diabetes. In the United Kingdom Prospective Diabetes Study (UKPDS), a major risk factor for CVD in type 2 diabetes included systolic blood pressure.13 Blood pressure was also observed to be a strong CVD risk factor in patients with type 2 diabetes in the Prospective Cardiovascular Munster (PROCAM) study.24 There is an increasing body of data from controlled clinical trials indicating that rigorous control of blood pressure to levels below the conventional control levels of less than 140/90 mm Hg markedly reduces CVD and stroke morbidity/mortality as well as development of ESRD in persons with type 2 diabetes.25—30 For example, in the UKPDS,25 in patients assigned to “tight” blood pressure control (144/82 mm Hg), there were significant reductions in diabetes—related end points, in death—related end points due to diabetes, in strokes, and in microvascular end points, especially diabetic retinopathy23 (Figure 3). Furthermore, the relative benefit on CVD risk reduction was more powerful for intensive blood pressure reduction than for tight glucose control. The Hypertension Optimal Treatment (HOT) study29 reported that in a diabetic subgroup (n = 1501), major CVD events were reduced by 51% in those randomized to a diastolic blood pressure goal of less than 80 mm Hg compared with a goal of less than 90 mm Hg (Figure 4). In a placebo—controlled trial of treatment of isolated systolic hypertension, the Systolic Hypertension in Europe (Syst—Eur) trial,27 the 492 patients with diabetes were reported in a post hoc analysis to have significant reductions in CVD mortality, all CVD events, and stroke with a reduction in mean systolic pressures from 175 to 153 mm Hg. These data from the

Table 1. Mechanism of Insulin Resistance in Hypertension

<table>
<thead>
<tr>
<th>Mechanism of Insulin Resistance</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased glucose metabolism</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Increased oxidative stress</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Altered muscle fiber type</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Increased adipose tissue</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Decreased slow—twitch insulin—sensitive muscle fibers</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Increased reactive oxygen species</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Reduced generation of nitric oxide</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Vascular rarefaction</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Vascular hypertrophy</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Increased vasoconstriction</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

Figure 3. United Kingdom Prospective Diabetes Study 38,25 CVD indicates cardiovascular disease.
Syst-Eur trial are consistent with that of the Systolic Hypertension in the Elderly Program (SHEP) study, in which elderly persons with type 2 diabetes derived more CVD reduction compared with those without diabetes. In general, patients with diabetes in these clinical trials required more antihypertensive agents (1 of 3 treatments) compared with those without diabetes. In general, patients with diabetes in these clinical trials required more antihypertensive agents (1 of 3 medications) to achieve these more aggressive goals.

STROKE IN PATIENTS WITH TYPE 2 DIABETES AND HYPERTENSION

Stroke is the third leading cause of death in the United States. There are more than 700,000 strokes annually and more than 4.5 million stroke survivors. Diabetes is a well-documented independent modifiable stroke risk factor of increasing importance as the prevalence of diabetes increases. Indeed, the incidence of stroke among patients is up to 3 times that in the general population with an especially high-risk rate in the southeastern United States. There is an increase in both short- and long-term mortality in patients with diabetes following stroke. High admission glucose levels are one predictor of poor outcomes in these patients.

Since the incidence of stroke is higher and the clinical outcome poorer in patients with diabetes, prevention of this problem is important. Hypertension, heart failure, and cigarette and alcohol use are modifiable risk factors for stroke in patients with and without diabetes. In 8 years of observation in the UKPDS group, increased risk of stroke was strongly associated with systolic hypertension as well as atrial fibrillation.

Intervention trials have provided support for rigorous blood pressure control in prevention of stroke in patients with diabetes. In the UKPDS for combined fatal and nonfatal stroke, tight blood pressure control (mean blood pressure achieved, 144/82 mm Hg) resulted in a striking 44% relative risk reduction compared with less aggressive control (mean blood pressure of 154/87 mm Hg). This 44% risk reduction in stroke was even greater than 20% with antihypertensive treatment found in the diabetic cohort in SHEP. Data from the Syst-Eur trial with nitrendipine-based antihypertensive therapy showed that the excess risk of stroke associated with diabetes was abolished by antihypertensive treatment in older patients with type 2 diabetes and isolated hypertension. In the MICRO-HOPE subanalysis of the Heart Outcomes Prevention Evaluation (HOPE) study, 367377 patients with diabetes treated with ramipril showed a reduction of primary combined end points of myocardial infarction, stroke, and CVD death by 25% and a stroke reduction by 33%.

Recent studies have shown the beneficial effects of an angiotensin receptor blocker (ARB) and an angiotensin-converting enzyme/diuretic combination in reduction of primary and secondary strokes in high-risk patients, including those with diabetes. The recent Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) also showed that treatments using a diuretic and lowering systolic blood pressure were very important strategies to reduce stroke incidence in patients with diabetes. These data support recent guidelines recommending a blood pressure of less than 130/80 mm Hg in patients with diabetes and hypertension (Figure 5). However, there have been no controlled clinical trials that have clearly shown the benefits of treating to a blood pressure goal of 130/80 mm Hg.

LIFESTYLE CHANGES IN TREATMENT OF HYPERTENSION IN PATIENTS WITH DIABETES

An integral component of management of hypertension in patients with diabetes is the institution of lifestyle changes. Lifestyle changes emphasizing diet and exercise have been shown to prevent the development of type 2 diabetes in persons with im-

Figure 4. Events in patients with diabetes mellitus at baseline in relation to tight diastolic pressure control (HOT Trial). CV indicates cardiovascular; MI, myocardial infarction.

Figure 5. Treatment algorithm: antihypertensive therapy in the patient with diabetes. In patients with a creatinine level of 1.8 mg/dL or greater (≥159 µmol/L), thiazide diuretics are not effective and loop diuretics may be substituted. ARBs indicates angiotensin receptor blockers; ACE, angiotensin-converting enzyme; MI, myocardial infarction.
paired glucose tolerance.51,52 In addition to improving glycemic control, a diet that is high in fiber and potassium and lower in saturated refined carbohydrates and salt can improve the lipid profile and significantly lower blood pressure.43 Thus, to address risk factors for CVD in patients with diabetes, institution of lifestyle intervention strategies for reducing risk in this population is important.

Table 2. Cardiovascular Disease Risk Factors Associated With Cardiometabolic Syndrome

<table>
<thead>
<tr>
<th>1. Hypertension</th>
<th>4. Endothelial dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Central obesity</td>
<td>5. Low high-density lipoprotein cholesterol levels</td>
</tr>
<tr>
<td>3. Hyperinsulinemia/insulin resistance</td>
<td>6. High triglyceride levels</td>
</tr>
<tr>
<td>8. Small, dense low-density lipoprotein cholesterol particles</td>
<td>7. Increased apolipoprotein B levels</td>
</tr>
<tr>
<td>10. Increased fibrinogen levels</td>
<td>11. Increased C-reactive protein level and other inflammatory markers</td>
</tr>
<tr>
<td>12. Increased plasminogen activator inhibitor 1 and decreased plasminogen activator levels</td>
<td>13. Absent nocturnal dipping of blood pressure and heart rate</td>
</tr>
<tr>
<td>14. Salt sensitivity</td>
<td>15. Left ventricular hypertrophy</td>
</tr>
<tr>
<td>16. Premature/excess coronary artery disease, stroke, and peripheral vascular disease</td>
<td></td>
</tr>
</tbody>
</table>

As mentioned, hypertension is a powerful promoter of hypertension, type 2 diabetes, and hyperinsulinemia, which, in turn, may promote the development of diabetic nephropathy.5,11,42-52 Indeed, microalbuminuria has been associated with insulin resistance and hyperinsulinemia,52 atherogenic dyslipidemia,11,52 and the absence of a nocturnal drop in systolic and diastolic blood pressure11 and has been identified as a part of the cardiometabolic syndrome11,14 (Table 2). Because microalbuminuria is part of the cardiometabolic syndrome and is related to endothelial dysfunction and increased oxidative stress,5,11,53 it is not surprising that diabetic glomerulosclerosis parallels the process of diabetic atherosclerosis11 and is a powerful risk factor for CVD and stroke.11,54 Thus, even after adjustment for renal function, microalbuminuria remained a strong risk factor for CVD in a sub-analysis of the HOPE trial.55 In the HOPE trial, the presence of albuminuria doubled the risk for the composite end point of myocardial infarction, stroke, or CVD death and all-cause mortality. The risk of heart failure was 3.7 times greater in type 2 diabetic patients with microalbuminuria than in those without albuminuria.51 Furthermore, the risks of the composite end points, all-cause mortality, and heart failure hospitalizations in diabetic patients with microalbuminuria was significantly reduced with treatment with the angiotensin-converting enzyme (ACE) inhibitor ramipril.51

Several studies have provided evidence for unique benefits of antihypertensive agents that interrupt the renin-angiotensin system. The Collaborative Study Group compared the ACE inhibitor captopril with conventional antihypertensive therapy in patients with type 1 diabetes and nephropathy.50 Captopril treatment reduced the risk of a doubling of serum creatinine level and the combined end points of death and ESRD by approximately one half. The renoprotective effect of captopril was observed to be greater than would be expected from blood pressure reduction alone. Recent studies have addressed renal protection in type 2 diabetes. The Irbesartan Diabetic Nephropathy Trial (IDNT) evaluated the effects of irbesartan in 1715 patients with hypertension, type 2 diabetes, and pro-
teinuria, with urinary protein excretion of 900 mg/d or greater. These patients were randomized to the ARB irbesartan, placebo control, or amloidipine group, with an average follow-up of 2.0 years. The time event for composite end point of a doubling of serum creatinine level, ESRD, or death was 28% in the control group vs 19.8% in the irbesartan group (20% reduction, P = .02). Amloidipine treatment was associated with a 25.2% reduction in composite end points, which was not different from the control group but less than the irbesartan group (P = .006) (Table 3).

In another trial, the Reduction in End Points in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL) Study, the ARB losartan, 50 to 100 mg, plus conventional hypertensive therapy was compared with placebo plus conventional hypertensive therapy in 1513 patients. Serum creatinine levels were required to be between 1.3 to 3.0 mg/dL (114.9-265.2 µmol/L) and urine albumin-creatinine ratio had to be greater than 300 mg/g or 25 mg/mmol. The blood pressure goal was 140/90 mm Hg 3 months after randomization; additional antihypertensive agents, except ACE inhibitors and dihydropyridine calcium channel blockers, were allowed to achieve that goal. The primary end point of the trial was defined as the occurrence of a UAER higher than 200 µg/min and/or a UAER at least 30% higher than baseline on at least 2 consecutive measurements. Average blood pressure values were slightly lower in the 2 groups treated with irbesartan than in the placebo group during the first 6 months of the study, but this small difference disappeared during the last 12 months of the study. Subjects were followed for an average of 2 years. In the irbesartan (150 mg/d) group vs placebo, there was a 39% reduction (P = .08 [nonsignificant]) in the development rate of clinical proteinuria, while in the irbesartan (200 mg/d) group there was a 70% reduction in the primary end point (Table 3). Return to a normal UAER status after 24 weeks with valsartan vs amloidipine therapy. These differences were observed in association with equivalent blood pressure–lowering effects of the 2 agents, again emphasizing the unique beneficial effects of ARBs on the diabetic kidney.

There have also been trials examining the impact of combination of an ACE inhibitor and an ARB on diabetic nephropathy.61,62 For instance, in the Candesartan and Lisinopril Microalbuminuria (CALM) trial, a randomized study of the effect of combining the ARB candesartan and the ACE inhibitor lisinopril on microalbuminuria was conducted in 199 patients with type 2 diabetes. This was a 12-week combination therapy trial, with 12 weeks of prior monotherapy with either candesartan or lisinopril. In this study, the reduction in the urinary albumin-creatinine ratio in those receiving candesartan, 16 mg/d, and lisinopril, 20 mg/d, was significantly greater (50% reduction) than that observed with either agent alone (24% for candesartan and 39% for lisinopril). As is often the case with combination therapy, blood pressure values were lower compared with therapy with the individual

Table 3. Relative Risk Reductions in Angiotensin Receptor Blocker Nephropathy/CHD Studies

<table>
<thead>
<tr>
<th>End Point</th>
<th>IDNT (Irbesartan vs Amlodipine)</th>
<th>IDNT (Amlodipine vs Placebo)</th>
<th>RENAA (Losartan vs Placebo)</th>
<th>IRMA-2 (Irbesartan vs Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 × Creatinine level</td>
<td>37% (P &lt; .001)</td>
<td>-6% (P = .60)</td>
<td>25% (P = .006)</td>
<td>33% (P = .03)</td>
</tr>
<tr>
<td>2 × Creatinine level, ESRD, or death</td>
<td>23% (P = .006)</td>
<td>-4% (P = .89)</td>
<td>16% (P = .02)</td>
<td>20% (P = .02)</td>
</tr>
<tr>
<td>ESRD</td>
<td>23% (P = .07)</td>
<td>0% (P = .99)</td>
<td>28% (P = .002)</td>
<td>23% (P = .07)</td>
</tr>
<tr>
<td>Death</td>
<td>-4% (P = .8)</td>
<td>12% (P = .4)</td>
<td>-2% (P = .88)</td>
<td>8% (P = .57)</td>
</tr>
<tr>
<td>Cardiovascular morbidity and mortality</td>
<td>-3% (P = .79)</td>
<td>12% (P = .29)</td>
<td>10% (P = .26)</td>
<td>9% (P = .4)</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; ESRD, end-stage renal disease; IDNT, Irbesartan Diabetic Nephropathy Trial; IRMA-2, Irbesartan Microalbuminuria 2 trial; RENAA, Reduction in End Points in NIDDM With the Angiotensin II Antagonist Losartan study.


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agent, which makes interpretation of the findings difficult. After 24 weeks of therapy, diastolic blood pressure was reduced to a greater degree with combination therapy (−16.3 mm Hg) than with either candesartan (−10.4 mm Hg) or lisinopril (−10.7 mm Hg) alone.

CONCLUSIONS

Diabetic nephropathy is a global problem of significant economic consequence. To date, there is not an established means to predictably reduce the primary rate of development of diabetic nephropathy; rather, current practice typically addresses diabetic nephropathy when it is already present, either in the form of microalbuminuria or as the more advanced disease state characterized by macroproteinuria and declining renal function. Important elements of the treatment plan for diabetic nephropathy include meticulous blood pressure control and reduction in urine protein excretion to below 1 g/d. In this regard, ACE inhibitors and/or ARBs are of considerable importance. Currently, in type 1 diabetic nephropathy, ACE inhibitors remain the initial agents of choice, and if this class of drugs is poorly tolerated, ARBs can be substituted. In the instance of type 2 diabetic nephropathy, the available evidence supports the preferential use of ACE inhibitors and ARBs. However, to accomplish blood pressure goals in patients with diabetes and hypertension often requires the use of a low-dose diuretic as part of the treatment regimen

Accepted for publication July 25, 2003.

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