ABSTRACT

Diabetes and hypertension are 2 of the most potent risk factors for the development of cardiovascular disease, and they rarely exist in isolation. In fact, hypertension and diabetes are inextricably linked—most patients with diabetes have hypertension and a significant proportion of hypertensive patients become diabetic. If we are to prevent the link between developing hypertension and type 2 diabetes, it is necessary to understand how hypertension, diabetes, and excess weight are related. This article reviews the pathophysiologic mechanisms involved in patients with hypertension and diabetes, and how they invoke a complex interplay among the renin-angiotensin-aldosterone system, the sympathetic nervous system, the endothelium, the kidneys, and glucose metabolism. The current guidelines for preventing and managing hypertension in patients with type 2 diabetes are also briefly reviewed. In recent years, we have learned that hypertension can be prevented or effectively managed in patients with type 2 diabetes, utilizing the detailed recommendations from several established professional organizations to the wide range of currently available drugs. Our increasing understanding of the complex pathophysiology highlights why it is imperative that we must aggressively manage blood pressure in patients with type 2 diabetes.

INTRODUCTION

Diabetes and hypertension are 2 of the most well-known and potent risk factors for cardiovascular disease (CVD) development, and they rarely exist in isolation. Hypertension is a highly prevalent condition among the general population, affecting 1 in 3 adult Americans. In fact, the lifetime risk of developing hypertension is greater than 90%.

Hypertension in patients with diabetes is common, but there are important differences between hypertension in type 1 versus type 2 diabetes. Most patients with type 2 diabetes have essential hypertension, whereas patients with type 1 diabetes often have hypertension secondary to nephropathy. Hypertension is both a cause and consequence of nephropathy, creating an unfavorable prognosis for patients with diabetes. In fact, diabetes is now the leading cause of chronic kidney disease (CKD) leading to dialysis in the United States.

As hypertension and type 2 diabetes are frequent comorbidities, it is necessary to understand how they are related and how important it is to maintain optimal blood pressures in patients with diabetes.
THE PATHOPHYSIOLOGY OF HYPERTENSION AND DIABETES

Patients with diabetes are at increased risk of hypertension and as many as 80% of patients with type 2 diabetes will die of macrovascular disease. Nonetheless, not all hypertensive patients will develop hyperinsulinemia, and not all hyperinsulinemic patients develop hypertension.

Hypertension and glucose intolerance are part of the metabolic syndrome. Each of the components of the metabolic syndrome are independent risk factors for CVD and CKD, and their effects as risk factors are additive when present at the same time. Ultimately, hypertension leads to end-organ damage in the kidney, heart, and brain (Figure 1). In the presence of diabetes, these pathophysiologic effects are accelerated.

Hypertension in patients with type 2 diabetes results from a complex pathophysiologic interplay that includes the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system, the endothelium, the kidneys, and glucose metabolism, along with other mechanisms that are under investigation (eg, left ventricular hypertrophy, cardiac hyperreactivity, dyslipidemia, and cell membrane ion exchange).

ACTIVATION OF RAAS AND SYMPATHETIC NERVOUS SYSTEM

The RAAS is a pathophysiologic cornerstone in the hypertensive disease process. Renin is an enzyme that cleaves angiotensinogen to produce an inactive peptide (angiotensin I), which is converted by the angiotensin-converting enzyme (ACE) and other enzyme systems to angiotensin II, a potent vasoconstrictor. In addition to its well-known effects on vascular resistance, angiotensin II also induces cell growth in the arterial wall and cardiac myocyte and increases oxidative stress; it is also proinflammatory and thrombogenic.

Angiotensin-converting enzyme also inactivates bradykinin, a peptide that stimulates the release of nitric oxide, which counteracts the effects of angiotensin II by promoting vascular smooth muscle relaxation. Thus, ACE inhibitors have 2 effects—reducing the production of angiotensin II and preserving bradykinin, which has biological actions that oppose those of angiotensin.

The RAAS is controlled by the sympathetic nervous system (SNS), which is activated by many factors associated with type 2 diabetes, including hyperinsulinemia, excess weight, and an unhealthy diet. The Normative Aging study, involving a population-based cohort followed in Boston, found that SNS activity was elevated with hyperinsulinemia and that activation also correlated with body mass index (BMI). Numerous investigators have shown that obese subjects have elevated SNS activity, measured both directly and indirectly. Both human and animal studies have shown that food intake (primarily fat and carbohydrates) increases SNS activity, whereas fasting and weight loss decrease the activity. Insulin is believed to partially mediate the effect of diet by stimulating glucose uptake and metabolism and ultimately disinhibiting sympathetic neurotransmission from the brain stem. Several investigators have found that numerous other mechanisms and mediators are thought to cause SNS activation in the insulin-resistant state, including renal afferent nerve stimulation by increased intrarenal pressure, plasma free fatty acids, and increased sympathetic activity.

Figure 1. The Pathophysiologic Sequelae of Hypertension: Target Organ Damage

acids, and angiotensin II. The RAAS has been shown to play an important role in insulin sensitivity. Two large trials of ACE inhibitors (Heart Outcomes Prevention Evaluation and Captopril Prevention Project) showed that this class of drugs decreased the risk of developing type 2 diabetes in patients with hypertension and/or vascular diseases.

**Endothelial Dysfunction and Inflammation**

The endothelium has been described as “the organ that bridges several cardiovascular risk factors (eg, hypertension, dyslipidemia, smoking, diabetes, and congestive heart failure)” and may be the crystallizing nucleus for the development of vascular inflammation and atherosclerosis. The endothelium is responsible for maintaining the balance between vasoconstriction and vasodilation by producing compounds that regulate vascular homeostasis, among them angiotensin II and nitric oxide. The endothelium also helps to maintain normal blood viscosity by balancing clotting factors.

Endothelial dysfunction involves impaired vasomotor response (reduced vasodilation and increased endothelium-dependent contraction), cell proliferation, platelet adhesion/aggregation, vascular permeability, and vascular inflammation by stimulating production of adhesion molecules, growth factors, and vasoconstricting agents. Nitric oxide is a vasodilator. Reactive oxygen species, created during inflammation, impair vascular relaxation by reducing nitric oxide and increasing vascular contractile responses.

Activation of the RAAS also leads to endothelial dysfunction and inflammation by promoting production of angiotensin II, which induces vascular injury through several mechanisms, including vasoconstriction, cell growth, oxidative stress, and inflammation (inducing release of cytokines and proinflammatory transcription factors), all of which contribute to the prothrombotic state and plaque buildup and instability, and ultimately plaque rupture.

Angiotensin II is also one of the main mediators of the RAAS system, thus it is a continuous feedback loop.

Hypertension and insulin resistance contribute to endothelial dysfunction and inflammation in the vascular wall as well as smooth muscle cell proliferation, extracellular matrix deposition, cell adhesion, and thrombus formation, all processes that lead to atherosclerosis. Thus, the relationship between RAAS, endothelial dysfunction, and hypertension magnifies pathophysiologic risk in which continued promotion of endothelial dysfunction increases hypertension and elevated vascular resistance, and the activation of the RAAS exacerbates endothelial dysfunction.

**Risk Factors and Risk Stratification for Cardiovascular Disease**

Diabetes is the most impactful risk factor for CVD, followed by systolic blood pressure, smoking, and dyslipidemia. Most importantly, hypertension is one of the most modifiable risk factors for chronic heart disease, stroke, congestive heart failure, end-stage renal disease, and peripheral vascular disease. Data from the National Health and Nutrition Examination Survey (NHANES) have shown that more than 66% of the US adult population is now overweight or obese and the prevalence is rising at an alarming rate. The Centers for Disease Control and Prevention reports that in 2006, only 4 states had a prevalence of obesity less than 20%. Twenty-two states had a prevalence of obesity equal or greater than 25%; 2 of these states (Mississippi and West Virginia) had a prevalence of obesity equal to or greater than 30%. The vast majority of patients with type 2 diabetes are overweight or obese.

Besides increased work demanded of the heart, obesity is associated with activation of the RAAS, endothelial dysfunction, and renal dysfunction. Moreover, the NHANES data also showed that there is a direct linear relationship between BMI and systolic and diastolic blood pressure. In addition, a short-term study of 25 obese patients showed that with weight loss came significant reductions in plasma renin activity, aldosterone, and mean arterial pressure. However, not all forms of obesity are created equal. Visceral adiposity, in particular, is especially harmful with respect to cardiovascular risk. Visceral adipocytes are metabolically active, and visceral tissue is considered to be an endocrine tissue. Visceral adipocytes stimulate several pathophysiologic processes, including inflammation, hypertension, and renal injury, and they reduce thrombolysis by producing inflammatory cytokines, angiotensinogen, ACEs, and the angiotensin I receptor. Visceral adipocytes are also insulin resistant.

Recall that the RAAS can be activated centrally by increased free fatty acids, which increase aldosterone levels in the insulin resistance state; it can also be activated by adipose tissue. Angiotensin II, ACE levels, and plasma renin activity correlate with BMI.
Visceral adiposity contributes to hypertension through several mechanisms, including RAAS activation, increased SNS activity, sodium retention and volume expansion, progressive CKD, and inhibition of insulin signaling. Therefore, 1 important mechanism of preventing hypertension in patients with type 2 diabetes is weight control.

GUIDELINES FOR TREATMENT OF HYPERTENSION IN TYPE 2 DIABETES

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure continued the trend over the past few decades toward more aggressive detection and management of hypertension. A new category was created—“prehypertension”—in the hopes of identifying those prone to hypertension and preventing hypertension in the future. As shown in Figure 2, prehypertension is defined as systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg. In patients with type 2 diabetes, drug therapy is warranted to achieve a target blood pressure of lower than 130/80 mm Hg due to the progressive increases in cardiovascular and renal risk seen at these values. A joint statement from the American Diabetes Association (ADA) and the American Heart Association (AHA) concurs with this more aggressive approach to treating hypertension in patients with type 2 diabetes, noting that rigorous blood pressure control is absolutely necessary for reducing the progression of diabetic nephropathy to end-stage renal disease. Blood pressure should be measured at every routine visit of a patient with diabetes, and those found to have systolic blood pressures higher than 130 mm Hg or diastolic blood pressure higher than 80 mm Hg should have their blood pressure confirmed on a separate day. The National Kidney Foundation has also issued guidelines for management of hypertension in patients with diabetes and CKD. They, too, recommend a target blood pressure of lower than 130/80 mm Hg in patients with diabetes and CKD stages 1 to 4.

All 3 guidelines also share some additional recommendations with regard to therapy, discussed in detail in the article by Dr. Bakris later in this monograph. In brief, patients with both diabetes and hypertension should be treated with an ACE inhibitor or an angiotensin receptor blocker. If one class is not tolerated, the other should be substituted. Other drug classes that should be added to achieve blood pressure targets and reduce CVD events include β blockers, thiazide diuretics, and calcium channel blockers. In fact, multiple agents are virtually always required to achieve blood pressure targets. In an analysis of several of the large hypertension clinical trials in which the goal blood pressure was lower than 135/85 mm Hg (e.g., patients with diabetes or renal impairment), on average, 3.2 medications were utilized to achieve target blood pressure.

The ADA/AHA also recommends that if ACE inhibitors, angiotensin receptor blockers (ARBs), or diuretics are used, renal function and serum potassium levels should be monitored within the first 3 months.

Figure 2. JNC-7 Classification and Management of Hypertension and Recommendations for Patients with Type 2 Diabetes

<table>
<thead>
<tr>
<th>Stage</th>
<th>SBP/DBP</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>SBP &lt;120 mm Hg or DBP &lt;80 mm Hg</td>
<td>Lifestyle modification</td>
</tr>
<tr>
<td>Target for T2DM</td>
<td>SBP &lt;130 mm Hg or DBP &lt;80 mm Hg</td>
<td>2-drug combination for most</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>SBP 120–139 mm Hg or DBP 80–89 mm Hg</td>
<td>2-drug combination for most</td>
</tr>
<tr>
<td>Stage 1</td>
<td>SBP 140–159 mm Hg or DBP 80–89 mm Hg</td>
<td>2-drug combination for most</td>
</tr>
<tr>
<td>Stage 2</td>
<td>SBP ≥160 mm Hg or DBP ≥100 mm Hg</td>
<td>2-drug combination for most</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; β B = β blocker; CCB = calcium channel blocker; DBP = diastolic blood pressure; JNC-7 = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; SBP = systolic blood pressure; T2DM = type 2 diabetes mellitus.

Data from US Department of Health and Human Services; American Diabetes Association; National Kidney Foundation.
If potassium levels are stable over a minimum of 2 visits, follow-up could occur every 6 months thereafter. In addition, orthostatic measurement of blood pressure should be performed in people with diabetes and hypertension when clinically indicated. For patients not achieving target blood pressure despite multiple-drug therapy, it is valuable to consider referral to a physician specializing in the care of patients with hypertension.36

Currently, pharmacotherapy for prehypertension is not yet recommended (Figure 2), and no antihypertensive medication is approved for use in prehypertension.8,35 However, a recent study—the Trial of Preventing Hypertension—suggests that ARBs may have some benefit as a preventive measure.39 In this study, 809 patients with prehypertension were randomized to receive candesartan or placebo for 2 years, but they were followed for 4 years. After 2 years of study treatment, the relative risk of developing hypertension was reduced by 66.3% in the candesartan group compared to placebo (P < .001). After 4 years of follow-up (2 years of study treatment followed by 2 years of placebo for all participants), the benefits remained—a 15.6% reduction in relative risk for those who had originally received candesartan (P < .007).39 Therefore, other trials with antihypertensive agents in this patient population are warranted, given these results.

Note that lifestyle modifications are an integral part of all treatment recommendations, for those with or without compelling indications, and are encouraged for those with normal blood pressure and prehypertensive blood pressure values. Lifestyle modifications for the prevention or management of hypertension should include weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products.

**INDIVIDUALIZED RISK FACTORS**

As with many other conditions, recognized guidelines provide a starting point for treatment strategies, but ultimately management must be tailored based on each patient’s individual composite of risk. For example, the use of aspirin in primary prevention of cardiovascular events continues to be questioned. The updated guidelines from the British Hypertension Society state that “doctors should not focus solely on blood pressure, but must also formally assess total risk of CVD and use multifactorial interventions, including statins and aspirin, to reduce it.”36 The ADA/AHA statement indicates that “aspirin therapy (75–162 mg/d) should be recommended as a primary prevention strategy in those with diabetes at increased cardiovascular risk, including those who are over 40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria).”36 Yet, others have called into question its widespread use in the absence of more data that address specific subpopulations (eg, those younger than age 50 years and older than age 70 years), especially considering the known adverse events associated with aspirin, including gastrointestinal hemorrhage.41

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**Figure 3. Diastolic and Systolic Blood Pressures as Risk Factors for Coronary Heart Disease Vary by Age**

<table>
<thead>
<tr>
<th>Age</th>
<th>DBP Hazard Ratio (95% CI)</th>
<th>SBP Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60 years</td>
<td>0.83 (0.71–0.98)†</td>
<td>1.24 (1.15–1.33)*</td>
</tr>
<tr>
<td>50–59 years</td>
<td>0.97 (0.81–1.16)</td>
<td>1.1 (0.99–1.21)</td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>0.95 (0.83–1.09)</td>
<td>1.42 (1.15–1.74)*</td>
</tr>
</tbody>
</table>

* P < .001.
† P < .05.

Hazard ratio was associated with a 10-mm Hg increase in blood pressure.

This study evaluated 3060 men and 3479 women between 20 and 79 years of age (Framingham Heart Study participants) who were free of coronary heart disease and were not on antihypertensive drug therapy at baseline. The results show a gradual shift from diastolic blood pressure (DBP) to systolic blood pressure (SBP) as predictors of chronic heart disease risk with advancing age.

CI = confidence interval.

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Although conventional risk calculators allow the clinician to determine cardiovascular risk based on parameters that are easily measured in a clinical setting (systolic blood pressure, age, sex, cholesterol concentration, presence of diabetes, and smoking history), one could argue that such formal calculations are unnecessary for patients with hypertension and CVD, diabetes, or overt end-organ damage because these patients will clearly benefit from a multifactorial approach to risk reduction.9

Moreover, it is important for the primary care clinician to recognize that hypertension and diabetes, although frequently comorbid, also show differences in prevalence in different populations, particularly based on age and ethnicity. For example, although hypertension increases in prevalence with age, the effect of hypertension on risk for coronary heart disease varies. In younger persons, diastolic high blood pressure poses a greater risk, but the risk is almost equally distributed between systolic and diastolic blood pressure as patients enter their 50s (Figure 3). By the time a person is at least 60 years old, systolic high blood pressure poses a higher risk for coronary heart disease (Figure 3).42

In addition, although hypertension affects all ethnicities, there are some well-known disparities. Analysis of the most recent NHANES database by Ong et al revealed an overall prevalence of hypertension of 29%, but higher prevalence in non-Hispanic blacks (39%) versus non-Hispanic whites (29%) and Mexican Americans (28%).43

Thus, for the individual patient in the physician’s office, approaches to prevention and management must be individualized based on the particular risk factors, clinical profile, and sociodemographic setting of the individual patient.

**Conclusions**

There is evidence that hypertension can be prevented or ameliorated in patients with type 2 diabetes. Undoubtedly, we have a wide range of currently available drugs and detailed recommendations from several established professional organizations to address this disorder with evidence-based medicine to support our treatment choices. Moreover, our depth of understanding the complex interplay among hypertension, obesity, type 2 diabetes, and renal dysfunction shows why it is imperative to aggressively manage blood pressure in patients with type 2 diabetes. However, if we are to prevent the link from developing between hypertension and type 2 diabetes, we have to also overcome the challenges in adherence to weight loss, dietary changes, and physical exercise. A tailored approach to both prevention and treatment of hypertension is required in this high-risk population.

**References**

14. Hall JE, Crook ED, Jones DW, et al. Mechanisms of obesity-


