ABSTRACT
In individuals with metabolic syndrome, the risk of developing renal and cardiovascular disease (CVD) is increased. Even in patients with impaired glucose tolerance or “prediabetes” who also have hypertension, hyperlipidemia, or other components of metabolic syndrome, the risk of CVD morbidity and mortality increases significantly. Other key components of metabolic syndrome include visceral obesity, dyslipidemia, and microalbuminuria. Collectively with diabetes and hypertension, the patient with this cluster of risk factors exhibits a state of metabolic and vascular dysregulation that may lead to premature CVD and progression to chronic kidney disease. Management of hypertension is essential to the improvement of CVD risk and renal outcomes. Lifestyle modifications and use of multiple antihypertensive agents, including those that inhibit the renin-angiotensin-aldosterone system, are integral.


Diabetes is an epidemic in the United States, currently affecting 6.3% of the population or approximately 18.2 million individuals. Hypertension affects approximately 50 million individuals, and is the primary diagnosis in approximately 35 million office visits in the United States. Hypertension and diabetes are elements of metabolic syndrome and increase the risk for development of cardiovascular disease (CVD). Other components of the metabolic syndrome are a cluster of medical problems, including visceral obesity, dyslipidemia, and microalbuminuria. Collectively with diabetes and hypertension, the individual with this diagnosis exhibits a state of metabolic and vascular dysregulation that amplify the risk of CVD and likelihood of progression to chronic kidney disease (CKD).

Hypertension is more common in persons with overt diabetes. However, the initial stages of development of insulin resistance/hyperinsulinemia or impaired glucose tolerance (IGT) increases the challenges in the management of hypertension.

Treating hypertension in patients with IGT and other components of metabolic syndrome requires knowledge of the basic pathophysiologic mechanisms. The presence of metabolic syndrome, even without overt diabetes, implies a state of inflammation, oxidative stress, and hypercoagulability that leads to endothelial dysfunction and subsequent CVD. The development of microalbuminuria, even in patients with IGT, heralds progression to CKD and is a risk factor for CVD. Therefore, intervention is now targeted at routine surveillance for microalbuminuria and inhibition of the renin-angiotensin-aldosterone system (RAAS).

Although clinicians have a large armamentarium of antihypertensive agents, medical therapy should be tailored to the specific needs of each individual. Differences in age, gender, and ethnicity should be taken into consideration. Upon diagnosis of metabolic
syndrome, lifestyle modifications must be first instituted because they are the foundations of therapy. Certain drugs may have adverse side effects, such as derangements in electrolyte and metabolic parameters, which may preclude their use or require closer monitoring.

This article reviews the current evidence and specific recommendations regarding nonpharmacologic and pharmacologic management of hypertension in the prediabetic population with other components of metabolic syndrome.

HYPERTENSION AND DIABETES

Hypertension and diabetes are predisposing risk factors for the development of CVD and renal disease. Hypertension frequently coexists with diabetes; the prevalence of hypertension in patients with type 2 diabetes is 3 times greater than in age- and sex-matched patients without diabetes. Furthermore, patients with documented hypertension are 2.5 times more likely to have diabetes than their normotensive counterparts.

The coexistence of hypertension and diabetes synergistically promotes the development of CVD and renal disease. When hypertension coexists with diabetes, the patient’s risk for CVD is increased by 75%, further contributing to the overall morbidity and mortality of an already high-risk population. Even relatively small increases in blood pressure are disadvantageous in patients with diabetes; a 10-mm-Hg increase in systolic blood pressure in a patient with diabetes produces a 15% increase in mortality caused by the diabetes, an 11% increase in acute myocardial infarction, a 19% increase in the incidence of strokes, and a 12% increase in episodes of congestive heart failure.

In addition, when these 2 conditions are present, the risk for developing end-stage renal disease (ESRD) is increased 5 to 6 times in comparison with those patients who have been diagnosed with hypertension, but are not diabetic. The development of CKD and progression to ESRD, in itself, is associated with compounded CVD risk.

In the development of hypertension in the diabetic population, increasing age, obesity, and the onset of renal disease all increase the likelihood of the development of CVD. Hypertension in patients with type 2 diabetes also occurs with other components of metabolic syndrome, such as microalbuminuria, central obesity, insulin resistance, and dyslipidemia.

METABOLIC SYNDROME

Metabolic syndrome is a grouping of risk factors that predict impending CVD. Within the United States and throughout the world, metabolic syndrome is an epidemic with significant health and economic consequences. Currently, the overall prevalence of the metabolic syndrome in the United States is 26.7% in men and women older than 20 years of age, up from 23.1% in the Third National Health and Nutrition Examination Survey (1988–1994). Furthermore, prevalence increases to 31.7% for ages 40 to 59 years and 42.5% for ages older than 60 years.

The National Cholesterol Education Program Adult Treatment Panel III (ATP III) defines the metabolic syndrome as presence of any 3 or more of the following:

- Blood pressure 130/85 mm Hg or higher
- Waist circumference greater than 40 inches in men and greater than 35 inches in women
- Triglyceride levels 150 mg/dL or higher
- High-density lipoprotein (HDL) levels less than 40 mg/dL in men and less than 50 mg/dL in women
- Fasting blood glucose levels 110 mg/dL or higher

The World Health Organization defines metabolic syndrome as insulin resistance (type 2 diabetes, impaired fasting glucose, or IGT) with any 2 of the following:

- Treatment with antihypertensive medication
- Systolic blood pressure greater than 140 mm Hg systolic or 90 mm Hg diastolic
- Plasma triglyceride levels 150 mg/dL or higher (1.7 mmol/L)
- HDL cholesterol less than 35 mg/dL (<0.9 mmol/L) in men or less than 39 mg/dL (1.0 mmol/L) in women
- Body mass index higher than 30 kg/m² and/or waist-to-hip ratio greater than 0.9 in men and greater than 0.85 in women
- Urinary albumin excretion rate 20 µg/min or albumin-to-creatinine (Cr) ratio 30 mg/g

In ATP III, specific underlying risk factors for the metabolic syndrome include obesity (especially centripetal obesity), a lifestyle of physical inactivity, and atherogenic diet. Major risk factors for CVD identified by ATP III include current cigarette smoking, presence of hypertension, a cholesterol profile consis-
tent with elevated low-density lipoprotein (LDL) levels and low HDL levels, a family history of premature coronary heart disease, and increasing age. Emerging risk factors are elevated triglyceride levels, elevated small LDL particle levels, insulin resistance, glucose intolerance, proinflammatory state, and prothrombotic state. Specific factors of metabolic syndrome that have been shown to increase the likelihood of development of hypertension, CKD, and ultimately CVD include abdominal obesity, dyslipidemia, and insulin resistance.

**MANAGING THE METABOLIC SYNDROME**

The initial step in the management of the metabolic syndrome is to first identify those who are at risk. Because, by definition, the syndrome consists of clustering of metabolic derangements, those who are identified as having 1 of the requirements for diagnosis should be screened for other aspects of the syndrome. The initial step should be obtaining a detailed medical history, including family illnesses, especially those pertaining to coronary artery disease and diabetes. In addition, aspects of the patient's personal habits, such as smoking, dietary preferences, and exercise frequency, should also be emphasized.

The patient's height and weight should also be recorded initially for body mass index calculation and to establish a baseline for further management. Blood pressure monitoring is essential. Waist circumference, measured at the narrowest point between the umbilicus and the rib cage, has been shown to be a better predictor of cardiovascular risk than waist-to-hip ratio.

In addition to patient history, laboratory data, including fasting lipid panel, fasting plasma glucose, dipstick for albumin in urine, and a hemoglobin A1c, should be obtained. With concern for glucose intolerance, 2 fasting blood sugars can also be obtained to provide additional data.

The goal of therapy in patients with metabolic syndrome is to prevent or delay the onset of type 2 diabetes and CVD. The individual components of the syndrome should be targeted. The cornerstone of therapy should begin with the adoption of a healthy lifestyle, which includes smoking cessation, regular exercise of at least 30 minutes 3 to 5 times a week, and weight loss. The benefits of these modifications are emphasized in the latest recommendations from the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), which stresses that changes in dietary and exercise habits are pivotal for the prevention and treatment of hypertension. Patients who have been diagnosed with metabolic syndrome should be encouraged to improve their dietary (e.g., eat more foods with omega-3 fatty acids, such as fish) and exercise habits as the initial step of therapy.

The benefits of adopting a healthier lifestyle through improved diet and exercise are well proven. In the Dietary Approaches to Stop Hypertension study, patients who were placed on a dietary regimen that emphasized foods low in saturated fats and rich in fruits, vegetables, and low-fat dairy products, with or without sodium restrictions, had a significantly reduced blood pressure. In addition, reductions were significantly greater in hypertensives than in normotensives. Increased physical activity also plays a beneficial role in therapy. In the Finnish Diabetes Prevention study, overweight patients with glucose intolerance who received intensified lifestyle intervention, which consisted of diet and moderate exercise for at least 30 minutes per day, showed not only a marked reduction in the risk of developing type 2 diabetes, but also a significant drop in blood pressure. In patients who find weight loss to be difficult, exercise and dietary changes that act to lower blood pressure and improve lipid levels will also improve insulin resistance, even in the absence of weight loss.

**PHARMACOLOGIC TREATMENT OPTIONS**

**ANGIOTENSIN-CONVERTING ENZYME INHIBITORS**

Angiotensin II plays a significant role in insulin resistance and the progression of hypertension and CVD. The interruption of the RAAS can provide significant cardioprotective properties. Data from trials, such as the Captopril Prevention Project (CAPP), Heart Outcomes Prevention Evaluation (HOPE) trial, and its substudy, the Micro-HOPE, have all shown the benefits that angiotensin-converting enzyme (ACE) inhibitors can provide for CVD. In addition to these benefits for CVD, agents that disrupt the RAAS may have direct effects on improving insulin sensitivity and may prevent development of diabetes in patients with hypertension compared to other medications, such as β blockers. In the CAPP trial, there was a 14% reduction in the development of new-onset diabetes in patients receiving an ACE inhibitor compared to placebo.
to conventional therapy. In the HOPE trial, there was a 34% relative risk reduction for developing diabetes with the use of similar drugs.

In addition, ACE inhibitors are renoprotective, by decreasing the renal membrane’s permeability to albumin and by decreasing intraglomerular pressure.21,22 Ultimately, this reduction in microalbuminuria prevents the progression to CKD, and meta-analyses have shown that this antiproteinuric effect is independent of blood pressure reduction.23

When initiating therapy, renal function and serum potassium levels should be monitored carefully. Although a slight increase in serum Cr may be seen due to intravascular depletion,24 an increase in Cr levels of greater than 30% or levels that increase continuously during the first 2 months of therapy may indicate underlying pathology, such as renal artery stenosis or chronic volume depletion.21,24 Often, the elevated Cr levels will normalize with correction of volume status.24

**ANGIOTENSIN RECEPTOR BLOCKERS**

Angiotensin receptor blockers (ARBs) offer another group of medications that provide RAAS blockade. Specifically, these agents act to block the AT-1 receptor, which is responsible for the effects of angiotensin II.19,25,26 In addition, ARBs offer a more complete RAAS blockade, as ACE inhibitors may not completely block the conversion of angiotensin I to angiotensin II secondary to alternative pathway activation.27 In addition, the antihypertensive efficacy of ARBs is similar to that of ACE inhibitors, with an improved side-effect profile, most notably significantly lower rates of cough.28 As with ACE inhibitors, recent data have shown that ARBs reduce the risk of new-onset diabetes. In the Losartan Intervention for Endpoint reduction in hypertension study, a 25% reduction in the risk of new-onset diabetes was observed in the losartan group compared to the group that received β-blocker–based therapy.29 Similar results were also seen in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity trial, which reported a 22% reduction in the risk of new-onset diabetes in patients with heart failure when treated with candesartan.30

Similar to ACE inhibitors, ARBs also offer significant renoprotective measures. In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, in addition to the Irbesartan in Diabetic Nephropathy Trial, significant reductions in renal disease progression were shown and reduction in albuminuria and Cr doubling time.19,25 Furthermore, combined ACE inhibitor and ARB therapy has shown greater reduction in albuminuria, as displayed in the Candesartan and Lisinopril Microalbuminuria trial.31

As with ACE inhibitors, patients started on ARB therapy should be monitored closely after initiation of therapy, especially by measuring serum potassium and renal function indices. Because ARBs have similar effects on the vasculature as ACE inhibitors, the possibility of worsening of renal function exists in those patients who may have underlying renal stenosis or who are chronically volume depleted.

**THIAZIDE DIURETICS**

Although thiazide diuretics are among the oldest available antihypertensive agents, they still play a significant role in the management of hypertension, especially in metabolic syndrome. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), thiazide diuretics comparably reduced all-cause mortality, such as stroke, coronary artery disease, and heart failure, when compared with ACE inhibitors and calcium channel blockers (CCBs).32 In addition, results from ALLHAT show that thiazides should be considered as first-line therapy for many patients with hypertension, including those with diabetes and metabolic syndrome.21,22

Thiazides, at high doses, can lead to electrolyte disturbances, in addition to worsening of insulin resistance, and have adverse effects on lipid metabolism; this is less common with lower doses.32-34 The efficacy of thiazides is also limited by a reactive increase in renin and angiotensin II levels in response to reduced plasma volume, leading to sodium and water retention and vasoconstriction.35 This adverse effect may be overcome with combination therapy with an ACE inhibitor or an ARB secondary to RAAS blockade. The antihypertensive efficacy of each agent alone may be potentiated when used in combination.

**CALCIUM CHANNEL BLOCKERS**

Data compiled from clinical studies indicate that 65% of all patients with hypertension require at least 2 (often 3) antihypertensive agents to achieve a target blood pressure of less than 130/80 mm Hg.56,57 CCBs offer a proven second-line therapy as adjuncts to the agents mentioned earlier in this article.38 In addition to
their role in control of hypertension, CCBs also reduce insulin resistance or new-onset diabetes among people with hypertension.22,39 Furthermore, CCBs have also been shown to have renoprotective qualities. Although these agents do not offer the same degree of renal protection as ACE inhibitors when used in head-to-head monotherapy, combination therapy has shown to have additive effects in reducing albuminuria.40 The RENAAL study showed that dihydropyridine calcium antagonists, such as amlodipine and nifedipine, are renoprotective when used in combination with the agents that block the RAAS.26 The nondihydropyridine calcium antagonists, such as verapamil and diltiazem, have also been shown to have additional benefits of reducing proteinuria when used in combination with the RAAS blockers.41 Another added benefit of CCB therapy is their effect on lipid metabolism; a 7% to 10% increase in HDL cholesterol above baseline has been shown in patients with metabolic syndrome.42

β BLOCKERS

β blockers are also effective antihypertensive agents in the diabetic population, as demonstrated in the UK Prospective Diabetes Study (UKPDS). This study found that atenolol was comparable to captopril in reduction of blood pressure and cardiovascular outcomes.43 Nonetheless, their use has often been complicated with their associated adverse effects on glucose and lipid profiles, in addition to their implication in new-onset diabetes in obese patients.44,45 Further complicating their use is the propensity for vasospasm, and subsequent peripheral vasculature compromise.

However, nonselective β blockers, such as carvedilol, which have been shown to induce vasodilatation, have a role in therapy in metabolic syndrome because they improve hypertension control and have been found to have favorable effects on CVD outcomes, in addition to improvement in insulin sensitivity.46-48 Furthermore, agents such as carvedilol and atenolol have renoprotective qualities, as they have demonstrated reductions in albuminuria, especially when used in conjunction with a RAAS-blocking agent.49

COMBINATION THERAPY IN THE MANAGEMENT OF HYPERTENSION

According to recommendations of the JNC 7, a second drug from a different class should be initiated when a single agent in adequate doses fails to achieve the blood pressure goal.21 Patients who are initially diagnosed with blood pressure levels greater than 20/10 mm Hg above goal should receive initial therapy with 2 drugs, as separate agents or in fixed-dose combinations. The JNC-7 recommendations suggest using a combination that contains a diuretic. Several fixed-dose combination therapies are currently available for the treatment of hypertension (Table). Multiple agents with different inhibitory mechanisms are likely to be more effective by targeting the various underlying mechanisms that contribute to hypertension. The limitations of individual agents may be overcome by the counteractive feedback mechanisms of individual agents. In addition, doses are lower with coadministration of agents than when they are used as single agents.99 Fixed-dose combinations facilitate dosing and improve compliance, possibly allowing patients to achieve target blood pressure levels more quickly with initial therapy.

Several trials have shown that tight blood pressure control is associated with reductions in cardiovascular sequelae and end-organ damage. However, tight blood pressure control often requires the use of more than 1 drug. In the Hypertension Optimal Treatment study, in which 90% of patients with stage 2 or stage 3 hypertension achieved a diastolic blood pressure less than 90 mm Hg, 70% of patients received combination therapy.50 After 9 years of follow-up in the UKPDS, 29% of patients who were assigned to tight blood pressure control required 3 or more agents to lower blood pressure to target levels.43 Angiotensin receptor blockers and diuretics are well-established antihypertensive monotherapies. Hydrochlorothiazide is safe and effective when administered at daily doses of 25 mg or less.21 The ARBs have been shown to have cardio- and renoprotective effects independent of their blood-pressure–lowering effects.20,51,52 The results of ALLHAT indicated that thiazide diuretics were more effective in preventing heart failure than ACE inhibitors or CCBs.52 However, there were no significant difference between the treatments for the primary end points of fatal coronary disease or nonfatal myocardial infarction, and the study allowed other drugs to be added if blood pressure was not controlled.53 The Valsartan Antihypertensive Long-term Use Evaluation trial, in which most patients received a diuretic, showed a trend toward less heart failure with a valsartan-based treatment than with an amlodipine treatment. Although both regimens were associated with lowered blood pressure, amlodipine was associat-
ed with greater reductions than valsartan.\textsuperscript{51} Although controversy remains regarding the efficacy of various agents in the treatment of hypertension, it is clear that most patients require combination therapy and that low-dose diuretics should be a part of the treatment regimen. The combination of an ARB with hydrochlorothiazide has been shown to be at least as effective as combinations using other agents, such as ACE inhibitors and CCBs, with better tolerability.\textsuperscript{54,55}

**CONCLUSIONS**

Diabetes and hypertension are highly prevalent conditions that often coexist and contribute to metabolic syndrome and increased risk for CVD, in addition to renal disease. Several disorders characterize metabolic syndrome, providing clinicians with many challenges in the treatment of individuals with hypertension. Individual components of the syndrome

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\textsuperscript{*Some drug combinations are available in multiple fixed doses. Each drug dose is reported in milligrams. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HCl = hydrochloride; HCT = hydrochlorothiazide; LA = long acting. Reprinted with permission from Chobanian et al. Hypertension. 2003;42:1206-1252.\textsuperscript{21}
should be treated to prevent or delay the onset of type 2 diabetes and its complications. Lifestyle changes, such as smoking cessation, increased physical activity, and dietary modifications, have been shown to be effective components of therapy in patients with metabolic syndrome. Recently, the focus of pharmacologic therapy has shifted toward inhibition of the RAAS. Although ACE inhibitors and ARBs provide RAAS blockade, the ARBs, which were developed more recently, may offer more complete angiotensin II inhibition. In addition to their blood-pressure–lowering effects, the ARBs have been shown to reduce the risk for cardiovascular morbidity and mortality and also provide renoprotective benefits. The use of ARBs in combination with another drug from a different class may confer even greater benefits than use of either agent alone. The JNC 7 recommends including a diuretic as part of combination therapy.

REFERENCES


34. Arnes RP. A comparison of blood lipid and blood pressure responses during the treatment of systemic hypertension with indapamide and with thiazides. Am J Cardiol. 1996;77:12B-16B.


