Metabolic syndrome; treatment of hypertensive patients with this syndrome

Israelí, Zafar H.; Lyoussi, Badiàa; Hernández-Hernández, Rafael; Velasco, Manuel
Revista Latinoamericana de Hipertensión, vol. 1, núm. 3, julio-septiembre, 2006, pp. 8-23

Disponible en: http://www.redalyc.org/articulo.oa?id=170217081002
Introduction

Metabolic syndrome; treatment of hypertensive patients with this syndrome

Zafar H. Israili\(^1\), Badiâa Lyoussi\(^2\), Rafael Hernández-Hernández\(^3\), and Manuel Velasco\(^4\)

\(^1\)Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA
\(^2\)UFR Physiology – Pharmacology, Laboratory of Animal Physiology, Department of Biology, Faculty of Sciences Dhar El Mehraz, Fez, Morocco.
\(^3\)Clinical Pharmacology Unit and Hypertension Clinic, School of Medicine, Universidad Centroccidental "Lisandro Alvarado". Barquisimeto, Estado Lara, Venezuela
\(^4\)Department of Pharmacology, “JM Vargas” Medical School, Central University of Venezuela, Caracas, Venezuela

Address correspondence to:
Dr. Zafar H. Israili
Department of Medicine
Emory University School of Medicine
69 Jesse Hill Jr. Drive, Atlanta, Georgia, USA
Phone: 678-480-5860
Fax: 404-522-3799
E-mail: zisrail@emory.edu

Hypertension is no longer viewed as a case of isolated high blood pressure (BP) in a patient, but rather a complex pathology with associated risk factors and co-morbidities. More than 80% of individuals with stage I or greater hypertension (as defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; JNC-7)\(^1\) have additional comorbidities, which increase the risk of cardiovascular (CV) complications. At least 20% of hypertensive patients have at least three of the following comorbidities and/or CV risk factors: obesity, glucose intolerance, hyperinsulinemia, low levels of high-density lipoprotein (HDL)-cholesterol, elevated low density lipoprotein (LDL)-cholesterol and triglyceride levels, left ventricular (LV) hypertrophy, and tobacco use.\(^2\) When some of these individual CV risk factors cluster in an individual, the person is said to have metabolic syndrome (see below). Hypertension is the key component of the metabolic syndrome. Therefore, the aim of treatment of hypertension in a patient is not only to control high blood pressure (BP) but also to reduce the associated CV risk factors and treat other co-morbidities. Treatment of several of these risk factors simultaneously results in improvement in CV outcomes in individuals with established hypertension. This review discusses the metabolic syndrome and some of the options available in treating hypertensive patients with this syndrome.
Several separate working definitions of metabolic syndrome have been proposed, which differ in criteria and cutoff points:

1. World Health Organization:
   - Diabetes, impaired fasting glucose, impaired glucose tolerance, or insulin resistance (assessed by clamp studies) and at least two of the following criteria:
     - Waist-to-hip ratio > 0.90 in men or > 0.85 in women
     - Triglycerides > 1.7 mmol/L
     - HDL cholesterol < 0.9 mmol/L in men and < 1.0 mmol/L in women
     - BP > 140/90 mmHg
     - Urinary albumin excretion rate > 20 µg/min or albumin-to-creatinine ratio > 30 mg/g

   - Any 3 or more of the following criteria:
     - Waist circumference > 102 cm in men and > 88 cm in women
     - Triglycerides > 1.7 mmol/L
     - HDL cholesterol < 1.0 mmol/L in men and < 1.3 mmol/L in women
     - Fasting glucose > 6.1 mmol/L (110 mg/dL)
     - Later modified to > 5.6 mmol/L (100 mg/dL)

3. European Group for the Study of Insulin Resistance (EGIR):
   - Waist circumference > 102 cm in men and > 88 cm in women
   - Fasting glucose > 100 mg/dL
   - BP > 130/85 mmHg or medication
   - HDL-cholesterol < 40 mg/dL (men), < 50 mg/dL (women)
   - Triglycerides > 150 mg/dL

4. International Diabetes Federation (IDF):
   - Central obesity, defined as waist ≥ 94 cm for males and ≥ 80 cm for females
     - Japanese waist ≥ 90 cm for males and ≥ 80 cm for females
     - South Asians waist ≥ 90 cm for males and ≥ 80 cm for females
     - Together with 2 of the following:
       - Triglycerides ≥ 1.7 mmol/L (150 mg/dL)
       - HDL-cholesterol: < 40 mg/dL (men), < 50 mg/dL (women)
       - BP ≥ 130/85 mmHg
       - Fasting hyperglycemia (impaired fasting glucose), defined as glucose > 5.6 mmol/L (100 mg/dL) or previous diagnosis of diabetes or impaired glucose tolerance

The most widely used diagnostic criteria of the metabolic syndrome are according to NCEP/ATP III and WHO, while the EGIR and the new IDF definitions are also used by many investigators (Table 1).

However, the multiple definitions of the metabolic syndrome cause confusion particularly when comparing data from different studies. To remove some of the confusion, the International Diabetes Federation has proposed a unifying definition of the metabolic syndrome (Table 1), which is somewhat an amalgam of the three major definitions (WHO, EGIR, NCEP/ATP III), but it does not include insulin resistance in the criteria (http://www.idf.org/webdata/docs/ accessed August 2005; http://www.medscape.com/viewarticle/504382, accessed August 2005).

Table 1: Definitions of the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Definition</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCEP/ATP III</td>
<td>1) Waist circumference &gt; 102 cm in men and &gt; 88 cm in women; 2) triglycerides ≥ 1.7 mmol/L; 3) BP ≥ 130/85 mmHg; 4) HDL cholesterol &lt; 1.0 mmol/L in men and &lt; 1.3 mmol/L in women; 5) Fasting glucose &gt; 6.1 mmol/L (110 mg/dL), later modified to ≥ 5.6 mmol/L (100 mg/dL)</td>
</tr>
<tr>
<td>WHO</td>
<td>Diabetes, impaired fasting glucose, impaired glucose tolerance, or insulin resistance (assessed by clamp studies) and at least two of the following criteria: 1) Waist-to-hip ratio &gt; 0.90 in men or &gt; 0.85 in women; BMI &gt; 30 kg/m² 2) Triglycerides &gt; 1.7 mmol/L (150 mg/dL) or HDL-cholesterol &lt; 0.9 mmol/L (35 mg/dL) in men and &lt; 1.0 mmol/L (39 mg/dL) in women; 3) BP ≥ 140/90 mmHg; 4) Urinary albumin excretion rate &gt; 20 µg/min or albumin-to-creatinine ratio &gt; 30 mg/g</td>
</tr>
<tr>
<td>EGIR</td>
<td>1) Waist circumference &gt; 102 cm in men and &gt; 88 cm in women; 2) Fasting glucose ≥ mg/dL; 3) BP ≥ 130/85 mm Hg or medication; 4) HDL-cholesterol &lt; 40 mg/dL (men), &lt; 50 mg/dL (women); 5) triglycerides ≥ 150 mg/dL</td>
</tr>
<tr>
<td>IDF</td>
<td>Central obesity, defined as waist ≥ 94 cm for males and ≥ 80 cm for females; Japanese waist ≥ 90 cm for males and ≥ 80 cm for females; South Asians waist ≥ 94 cm for males and ≥ 80 cm for females; together with 2 of the following: a) Triglycerides ≥ 1.7 mmol/L (150 mg/dL) b) HDL-cholesterol, defined as &lt; 1.04 mmol/L (40 mg/dL) in males and &lt; 1.29 mmol/L (50 mg/dL) in females c) BP ≥ 130/85 mm Hg; and d) Fasting hyperglycemia (impaired fasting glucose), defined as glucose ≥ 5.6 mmol/L (100 mg/dL) or previous diagnosis of diabetes or impaired glucose tolerance</td>
</tr>
</tbody>
</table>
The major components of the metabolic syndrome are obesity, glucose intolerance, insulin resistance, low levels of HDL-cholesterol, elevated LDL-cholesterol and triglyceride levels, and elevated BP (Table 1). Hyperuricemia and hyperleptinemia have also been proposed as components of the metabolic syndrome. In addition, the metabolic syndrome has been associated with the following:

- A prothrombotic state (high fibrinogen, decreased fibrinogen activator and/or plasminogen activator inhibitor-1 in blood);
- A proinflammatory state (elevated high-sensitivity C-reactive protein, proinflammatory cytokines and adhesion molecules in the blood);
- Increased intima-media thickness;
- Decreased adiponectin levels;
- Low serum magnesium;
- High serum ferritin and iron overload;
- Polycystic ovary syndrome;
- Sleep apnea;
- Increased brachial-ankle pulse wave velocity;
- Low levels of androgens (testosterone and dehydroepiandrosterone) and sex-hormone binding globulin.

Metabolic syndrome is becoming increasingly common, with a prevalence of 10% to 30% of the adult population in industrialized countries, depending on the definition used (Table 2). It is estimated that 47 million Americans have metabolic syndrome; about 40% of adults age 50 or older have the metabolic syndrome. The prevalence rate increases with age, degree of obesity (body mass index), level of hyperglycemia, and the presence of hypertension; the prevalence of the syndrome among diabetics is quite high (70%-90%). Using the WHO definition, the prevalence of the metabolic syndrome in a Swedish population was higher in females than in males, while in others, males had a higher prevalence than females; in some studies no gender difference was noted. However, it may be realized that the prevalence of the metabolic syndrome and its components are dependent on the definition used for the different components.

**Table 2. Prevalence of metabolic syndrome in certain populations**

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Americans1</td>
<td>23.0%</td>
<td>43</td>
</tr>
<tr>
<td>Arab Americans3</td>
<td>28.0%</td>
<td>43</td>
</tr>
<tr>
<td>China1</td>
<td>9.8 - 17.8%</td>
<td>44</td>
</tr>
<tr>
<td>China2</td>
<td>10.2 - 15.7%</td>
<td>17</td>
</tr>
<tr>
<td>Europe3</td>
<td>14.2 - 15.7%</td>
<td>45</td>
</tr>
<tr>
<td>Europe3</td>
<td>5.0 - 36.0%</td>
<td>46</td>
</tr>
<tr>
<td>Finland3</td>
<td>22.2 - 38.8%</td>
<td>47</td>
</tr>
<tr>
<td>France1</td>
<td>11-16%</td>
<td>48</td>
</tr>
<tr>
<td>Greece1</td>
<td>24.5%</td>
<td>49</td>
</tr>
<tr>
<td>India1</td>
<td>22.9 - 39.9%</td>
<td>50</td>
</tr>
<tr>
<td>Israel1</td>
<td>26%</td>
<td>51</td>
</tr>
<tr>
<td>Japan1</td>
<td>10.3 - 30.2%</td>
<td>52</td>
</tr>
<tr>
<td>Korea1</td>
<td>20.8 - 26.9%</td>
<td>53</td>
</tr>
<tr>
<td>Korea1</td>
<td>5.2 - 9.0%</td>
<td>54</td>
</tr>
<tr>
<td>Mexico3</td>
<td>13.6%</td>
<td>55</td>
</tr>
<tr>
<td>Mexico1</td>
<td>26.6%</td>
<td>55</td>
</tr>
<tr>
<td>Mexico1</td>
<td>39.9 - 59.9%</td>
<td>56</td>
</tr>
<tr>
<td>Sweden3</td>
<td>10 - 15%</td>
<td>57</td>
</tr>
<tr>
<td>Turkey1</td>
<td>23.7 - 39.1%</td>
<td>58</td>
</tr>
<tr>
<td>USA1</td>
<td>24.1 - 27.0%</td>
<td>40</td>
</tr>
<tr>
<td>USA1</td>
<td>26.3 - 29.3%</td>
<td>59</td>
</tr>
<tr>
<td>USA1</td>
<td>24.7 - 30.3%</td>
<td>60</td>
</tr>
<tr>
<td>USA1</td>
<td>28.1%</td>
<td>61</td>
</tr>
<tr>
<td>USA3</td>
<td>21.0%</td>
<td>61</td>
</tr>
<tr>
<td>Venezuela1</td>
<td>31.2%</td>
<td>62</td>
</tr>
</tbody>
</table>

Criteria used to define the metabolic syndrome: 1) NCEP/ATP III; 2) CDS; 3) WHO; 4) EGIR.

**Figure 3.** Prevalence of metabolic syndrome (according to the WHO criteria) and its various components in various groups (first bar for males and the second bar for females): normoglycemic individuals (NG); subjects with impaired glucose tolerance (IGT); subjects with type 2 diabetes mellitus (DM). (Adapted from Isomaa et al.)
The disorder of insulin resistance is the most accepted unifying hypothesis to describe the pathophysiology of the metabolic syndrome, although, this concept has been challenged, and not every individual with this syndrome has insulin resistance. The biologic mechanisms at the molecular level between insulin resistance and metabolic risk factors aren’t fully understood and appear to be complex. A four-factor model (blood pressure, obesity, insulin resistance, and lipid profile) has been suggested, which relates all the components of the metabolic syndrome. Although, abdominal obesity is considered as a central element of the metabolic syndrome, obesity as a single factor has recently been proposed to unify all the risk factors related to the metabolic syndrome. Obesity is positively correlated with higher BP, fasting insulin, triglycerides, and negatively associated with HDL-cholesterol. Since, obesity is also associated with a prothrombotic state, increased BMI is associated with higher risk of myocardial infarction and coronary heart disease. Never-the-less, not all individuals who have the metabolic syndrome are obese, since non-obese people can have other components of the metabolic syndrome, such as high BP, low HDL-cholesterol, high triglycerides, insulin resistance, etc.

In general, the underlying causes of this syndrome are excess body weight (visceral/central/ android obesity), physical inactivity/sedentary lifestyle, an atherogenic diet (high carbohydrates, low fiber, high saturated fat), high alcohol intake, and smoking. The development of metabolic syndrome has been found to be inversely related to dietary intake of magnesium. Chronic work stress has also been reported to be associated with the development of metabolic syndrome, possibly due to the involvement of chronic stimulation of autonomic nervous system and neuroendocrine activity. Polycystic ovary syndrome has many features in common with the metabolic syndrome and the two syndromes may share common pathogenesis. The use of certain drugs (high dose diuretics, blockers, corticosteroids, oral contraceptives, antipsychotics, protease inhibitors and niacin), which promote weight gain and/or alteration of lipid or glucose metabolism, may also increase the risk of the development of the metabolic syndrome. A genetic predisposition to development of metabolic syndrome is also possible as a result of K121Q polymorphism of the ENPP1/PC-1 gene, which regulates insulin response, and is linked to obesity and type 2 diabetes. The K121Q polymorphism of the ENPP1/PC-1 gene is associated with insulin resistance/atherogenic phenotypes, including earlier onset of type 2 diabetes and myocardial infarction. The ACE gene insertion/deletion polymorphism is significantly associated with the metabolic syndrome. Other genetic bases of metabolic syndrome have also been suggested.
tions, such as nephropathy, retinopathy, and distal neuropathy. Patients with the metabolic syndrome are also at high risk for the development of many hypertension-associated target organ damage both in diabetic and non-diabetic patients. Patients with the metabolic syndrome have significantly higher prevalence of microalbuminuria compared to those without it (12.3% versus 4.7%; p = 0.004). Patients with microalbuminuria are at a higher risk of developing CV disease. The metabolic syndrome is also an important risk factor for the development of chronic kidney disease in people without diabetes; this risk is significant even after adjustment for other factors, and increases along with the number of metabolic syndrome risk factors present. This suggests that the metabolic syndrome directly contributes to the development of chronic kidney disease. The metabolic syndrome is also an important risk factor for developing chronic kidney disease in people without diabetes; this risk is significant even after adjustment for other factors, and increases along with the number of metabolic syndrome risk factors present. This suggests that the metabolic syndrome directly contributes to the development of chronic kidney disease. The metabolic syndrome is also an important risk factor for developing chronic kidney disease in people without diabetes; this risk is significant even after adjustment for other factors, and increases along with the number of metabolic syndrome risk factors present. This suggests that the metabolic syndrome directly contributes to the development of chronic kidney disease.

Table 3. Prediction of risks by NCEP/ATP III and WHO definitions of the metabolic syndrome*

<table>
<thead>
<tr>
<th>Definition</th>
<th>NCEP/ATP III</th>
<th>WHO</th>
<th>Population-attributable fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>1.27</td>
<td>1.37</td>
<td>~ 6-7%</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>1.65</td>
<td>1.93</td>
<td>12-17%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.99</td>
<td>2.60</td>
<td>30-52%</td>
</tr>
</tbody>
</table>

* As reported by Schillaci et al.,154 and Ford et al.88

Clinical significance of the metabolic syndrome

There is a difference of opinion in terms of the significance and utility of the metabolic syndrome in clinical practice. Those who favor that metabolic syndrome should be a definite diagnosis requiring special clinical management put forward the argument that the presence of metabolic syndrome (impaired fasting glucose and impaired glucose tolerance) effectively predicts the development of type 2 diabetes and CV disease, and that insulin resistance syndrome (another name for the metabolic syndrome) should be categorized as a specific medical diagnosis. Thus, a version of the metabolic syndrome (dysmetabolic syndrome X) has its own ICD-code (ICD-9 Code 277.7) for the diagnosis and clinical management, and it is recommended that this syndrome should be treated to reduce the risk of CVD and diabetes. There is even a journal named, “Metabolic Syndrome & Related Disorders,” dedicated to this entity. The American Heart Association and National Heart, Lung, and Blood Institute (USA) recommend that the metabolic syndrome should be diagnosed and treated initially with diet and exercise, and an aggressive global approach to screening and to the management of the metabolic syndrome should be taken to slow the growth of the syndrome throughout the United States and other countries with high prevalence of the metabolic syndrome. It may be noted that the metabolic syndrome is an incomplete predictor of absolute risk. To predict absolute risk for individuals, sometimes called ‘global risk,’ it is necessary to include all of the risk factors related to the outcome. For CV disease, these include age, gender, total cholesterol, HDL-cholesterol, triglycerides, BP, body mass index, glucose status, tobacco usage, and family history, depending on the risk-assessment algorithm employed.

However, an opposite view is that the metabolic syndrome cannot be a definite diagnosis, because of certain concerns regarding the definition of the metabolic syndrome, in that a) the criteria are ambiguous, poorly defined or incomplete, and the list of risk factors comprising the cluster (metabolic syndrome) is not according to one well-defined, uniformly accepted criteria and the rationale for thresholds are ill defined; b) insulin resistance as the unifying etiology is uncertain, as there is no solid evidence that insulin resistance is the main cause of the syndrome; c) the value of including diabetes (such as the WHO criteria) in the definition is questionable, and there is no clear basis for including or excluding other CV risk factors; d) the underlying pathophysiology of the syndrome is unclear, although, several CV disease risk factors may occur together, the risks with the “syndrome” appear to be no greater than the sum of its parts; e) the CV risk value is variable and dependent on the specific risk factors present, and the notion that the metabolic syndrome is a useful marker of CV risk above and beyond the risk associated with its individual components is uncertain; f) the medical value of diagnosing the syndrome is unclear and the treatment of the syndrome is no different than the treatment for each of its components.

To counteract the criticism, at least partially, the International Diabetes Federation has proposed a unifying definition of the metabolic syndrome, which is somewhat an amalgam of the three major definitions (WHO, EGIR, NCEP/ATP III) (see earlier). It is expected that the new definition may be used worldwide and remove some of the confusion, and facilitate early detection by routine screening, identifying those at high risk for developing CV disease and diabetes, and implementing more intensive management to reduce the long-term risk of CV disease and diabetes (http://www.idf.org/webdata/docs/ accessed August 2005). Never-the-less, the use of any metabolic syndrome definition is driven by the objective, such as epidemiological studies, clinical trials, assessment of intervention programs, public health campaigns, or clinical management of at-risk individuals.
Because of the complex etiology of the metabolic syndrome, a multi-targeted, integrated therapeutic approach is required to simultaneously treat all the risk factors, at first by lifestyle (behavioral) modification (weight control, diet, exercise, smoking cessation), based on the observations that weight control enhances lowering of LDL-cholesterol and reduces many other risk factors associated with the metabolic syndrome, and exercise decreases VLDL-cholesterol and LDL-cholesterol, increases HDL-cholesterol, and decreases markers of inflammation. If lifestyle modification is not sufficient to decrease the risk factors, then pharmacotherapy be added to treat simultaneously the conventional lipid (dyslipidemia) and non-lipid CV risk factors (high BP, glucose intolerance, prothrombotic state, etc.).

Optimal management of hypertensive patients with the metabolic syndrome requires that such patients be managed differently than patients who do not have the disorder, in that a multi-targeted, integrated therapeutic approach is required to simultaneously treat hypertension, obesity, lipid disorders and diabetes (if present), to fully protect CV, cerebrovascular and renal systems. Lifelong lifestyle modification (weight control, diet, exercise, smoking cessation) should be instituted to be followed by pharmacologic therapy in patients with the metabolic syndrome.

**a) Treatment of obesity/weight reduction**

Lifestyle intervention (exercise, prudent diet) and antiobesity drugs, such as Orlistat (selective lipase inhibitor), sibutramine (serotonin antagonist), and rimonabant (cannabinoid-1 receptor blocker), are useful for weight reduction. The antiobesity drugs often improve lipid profile (reduction in LDL-cholesterol, VLDL-cholesterol and triglycerides, and increase in HDL-cholesterol) in patients with dyslipidemia, improve glycemic control in diabetic patients, and decrease risk for CV disease.

**b) Treatment of dyslipidemia**

Lifestyle modification, cholesterol-lowering drugs, such as statins, and triglyceride-reducing drugs such as fibrates and niacin, and fatty acids of omega-3 series correct dyslipidemia. Antiobesity drugs are sometime used to treat severely obese patients. A statin should be used initially for hyperlipidemia unless contraindicated. Statins decrease total cholesterol, LDL-cholesterol, and triglycerides, improve endothelial function and fibrinolytic activity (by increasing fibrinogen activator and decreasing plasminogen activator inhibitor-1), and increasing thrombin activatable fibrinolysis inhibitor; they have no effect on glycemic control. As shown by large clinical trials, reduction in total cholesterol by statins results in a significant decrease in CV events and all-cause mortality. Statins can cause muscle cramps, rhabdomyolysis, and have the potential to cause or worsen congestive heart failure or diastolic dysfunction, but these may be reversed by the administration of coenzyme Q10. Fibrates [peroxisome proliferator-activated receptor (PPAR)-agonists] reduce LDL-cholesterol, VLDL-cholesterol and triglycerides, and increase HDL-cholesterol; they improve insulin sensitivity.

Combined statin and fibrate therapy is effective in patients with complex lipid disorders. Addition of ezetimibe, a cholesterol-absorption inhibitor, to fibrate therapy further reduced LDL-cholesterol by 23% compared to statin alone. In this regards, several drug combinations are being developed to aggressively treat dyslipidemia, including niacin/lovastatin, ezetimibe/simvastatin, atorvastatin/CETP inhibitor, statin/PPAR agonist, and extended-release niacin/simvastatin and pravastatin/aspirin.

**c) Treatment of diabetes**

First of all, multifactorial strategies should be adopted to prevent the development of diabetes in individuals with the metabolic syndrome. In randomized trials, lifestyle modification, antiobesity drugs, and drugs increasing insulin sensitivity (such as metformin) prevented the development of type 2 diabetes in subjects with impaired glucose tolerance. However, if diabetes is already present then aggressive treatment to control blood sugar should be instituted.

Metformin should be considered as the first drug for glucose control in patient with type 2 diabetes; sulfonylureas also improve glycemic control. Metformin and thiazolidinediones (such as pioglitazone and rosiglitazone, which improve insulin resistance) appear promising in the treatment of diabetic patients. However, metformin can cause lactic acidosis. Among other anti-diabetic drugs, acarbose, which inhibits postprandial hyperglycemia, can be helpful in preventing postprandial hyperglycemia. The PPAR agonists may alter the process of atherosclerosis in patients with the metabolic syndrome and type 2 diabetes.
diabetes. These agents have a beneficial effect on the heart: the fibrates (PPAR-β agonists) and insulin-sensitizing thiazolidinediones (PPAR-γ agonists) improve LV hypertrophy and diastolic function in normotensive diabetic patients. Pioglitazone improves LV diastolic function without an effect on LV mass in hypertensive patients in proportion to amelioration of insulin resistance and increase in the levels of adiponectin and matrix metalloproteinase-2 (MMP-2). The thiazolidinediones also have a favorable effect on BP. However, the use of thiazolidinediones may cause fluid retention, edema, and idiosyncratic hepatocellular injury.

d) Treatment of clotting disorders
Patients with the metabolic syndrome have several disorders of coagulation that makes it easier to form blood clots, which are often a precipitating factor in developing myocardial infarction. Such patients should generally be placed on daily low-dose aspirin therapy to help prevent such clotting events.

Hypertension is a key component of the metabolic syndrome. More than 50% of individuals with the metabolic syndrome have hypertension; patients with insulin resistance have a higher prevalence of hypertension compared with subjects without insulin resistance. In turn, up to 50% of hypertensive patients may have insulin resistance and other components of the metabolic syndrome. Elevated systolic and diastolic BP independently increases the risk of atherosclerosis and coronary heart disease; high BP may also exacerbate other metabolic abnormalities. Dyslipidemia, a strong predictor of CV disease, may also lead to the subsequent development of hypertension; control of BP often improves lipid profile.

The presence of the metabolic syndrome amplifies hypertension-related cardiac and renal target organ damage over and above the potential contribution of each single component of this syndrome. For example, hypertensive patients with the metabolic syndrome, as compared to those without it, have higher LV mass and greater prevalence of LV hypertrophy, a 2-fold higher CV event rate, increased risk of retinopathy and microalbuminuria, the later being an independent risk factor for CV death. Metabolic syndrome is also associated with large artery stiffness, a strong predictor of CV morbidity and mortality in hypertensive patients.

**Treatment of hypertension**

The recommended target BP level (JNC-7) in treated hypertensives with the metabolic syndrome is <140/<90 mm Hg. However, a substantial proportion of patients with the metabolic syndrome have diabetes and/or chronic kidney disease, and, for such individuals, the JNC-7 and ADA recommend a goal of <130/<80 mm Hg.

The first step in lowering BP should be lifestyle intervention [sodium restriction, weight control, exercise, smoking cessation and moderation of alcohol consumption (for those who smoke and/or drink), and consumption of an overall healthy diet], since such intervention has been shown to lower BP. Lifestyle modification can also prevent the development of new onset type 2 diabetes as shown by the Diabetes Prevention Program Research Group. However, for the overwhelming majority of patients with established hypertension, drug therapy is the mainstay of treatment and lifestyle modification is merely adjunctive.

Lifestyle changes (through dietary means such as weight loss and salt restriction) are also the best way to prevent or delay the onset of hypertension in prehypertensive individuals as was shown by the Trials Of Hypertension Prevention. However, the transition from prehypertension to hypertension is inevitable, since people who are prehypertensive have a very high risk (90%) of eventually developing hypertension. The selection of drugs should be tailored to the individual, taking into account the pathophysiological determinants of the metabolic syndrome present and the presence of comorbidity (Table 4).

<table>
<thead>
<tr>
<th>Table 4 Recommended Antihypertensive Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compelling Indication</td>
</tr>
<tr>
<td>Diuretic Blocker</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Post-myocardial infarction</td>
</tr>
<tr>
<td>High coronary disease risk</td>
</tr>
<tr>
<td>Recurrent Stroke prevention</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Microalbuminuria</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
</tbody>
</table>

* Low doses; #ACE = angiotensin converting enzyme; ARB = Angiotensin AT1-receptor blocker; CCB = Calcium channel blocker.

It has been recommended that antihypertensive therapy in hypertensive patients with the metabolic syndrome should begin with an angiotensin-converting enzyme (ACE) inhibitor, unless there is a compelling indication for another class of drug. A number of...
Several large clinical trials, including the Heart Outcomes Prevention Evaluation (HOPE) and MICRO-HOPE sub-study, have demonstrated that ACE inhibitors provide cardioprotective and renoprotective benefits beyond their effect on BP. These drugs also improve insulin resistance by increasing insulin-mediated glucose uptake, and hence may be especially appropriate in treating hypertensive patients with the metabolic syndrome. The other advantages of using the ACE inhibitors include absence of fatigue and many other adverse effects associated with blockers and diuretics. However, ACE inhibitors cannot be given to pregnant women in the second and third trimester. Among the adverse effects associated with the use of ACE inhibitors include the induction of cough (more in women than in men), and on rare occasions, angioneurotic edema. ACE inhibitors may also cause symptomatic hypotension in salt-and/or volume-depleted patients, and hyperkalemia in patients on potassium-sparing diuretics.

Several large clinical studies, such as the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, Irbesartan in Diabetic Nephropathy Trial (IDNT), Reduction of Endpoints in Non-insulin-dependent Diabetes Mellitus with the All Antagonist Losartan (RENAAL), and Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM)-Overall, and the Losartan Intervention For Endpoint reduction in hypertension study (LIFE), indicate that the ARBs, in addition to their renoprotective effect and excellent safety profile, are cardioprotective. Some ARBs (such as irbesartan and telmisartan) have partial PPAR-agonist activity, which makes them useful as antilipidemic, antiatherosclerotic and cardioprotective agents.

Traditionally, thiazide diuretics and blockers have been avoided in patients with glucose intolerance abnormalities, however, the safety and efficacy of these drugs has been demonstrated in large clinical trials (for example, the ALLHAT and UK Prospective Diabetes Study trials). Based upon these studies thiazides (at low doses) and -blockers have been recommended in hypertensive patients with the metabolic syndrome. In the ALLHAT study (randomized, double-blind, active-controlled clinical trial of hypertensive patients aged > 55 years who had one other risk factor for coronary heart disease), in which patients were randomized to receive either chlorthalidone, amlodipine, or lisinopril, plus open-label step-up drugs (reserpine, atenolol, clonidine, hydralazine or others) to reach goal BP, there was no difference between the drugs in the primary outcome in patients followed for a mean of 4.9 years (Figure 5). Furthermore, the presence or absence of metabolic syndrome did not make any difference in the control of BP (Figure 5). In the secondary outcomes, the diuretic was superior to the calcium channel blocker and ACE inhibitor. In a post hoc analysis, neither amlodipine nor lisinopril was superior to chlorthalidone in non-diabetic patients with or without the metabolic syndrome (Figure 6), although the diuretic was more likely to induce new-onset diabetes in both groups. In the UKPDS, atenolol was as good as captopril in target organ protection (stroke, heart failure, MI, total mortality).
Like the ACE inhibitors, the long-acting calcium channel blockers improve insulin sensitivity\(^{182}\). The results from a large number of clinical trials show no difference in the primary endpoints between -blockers/diuretics, calcium channel blockers and ACE inhibitors\(^{183}\). [Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT, n = 33,357)\(^{179}\); Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE, n = 16,602)\(^{184}\); International Nifedipine Gastrointestinal Therapeutic System study—Intervention as a Goal in Hypertension Treatment (INSIGHT, n = 6,321)\(^{185-187}\); INVEST = International Verapamil Slow-Release/Trandolapril Study (INVEST, n = 22,576)\(^{188}\); NORDIL = Nordic Diltiazem (NORDIL, n = 10,881)\(^{189}\); Swedish Trial in Old Patients with Hypertension (STOP-Hypertension-2, n = 66,144)\(^{190,191}\); United Kingdom Prospective Diabetes Study (UKPDS, n = 14,114)\(^{192}\); VHAS = Verapamil in Hypertension and Atherosclerosis Study (VHAS)\(^{192}\).]

Other drugs, such as celiprolol in combination with diuretics was found to have a favorable effect on glucose tolerance/insulin sensitivity in patients with essential hypertension and metabolic syndrome\(^{193}\), and spironolactone added to ACE inhibitor or ARB therapy had an added renol- and CV protective benefits in patients with diabetic nephropathy\(^{194}\). Carvedilol, a \(-\) blocker with vasodilating properties, added to ACE inhibitor or ARB therapy, was more effective in preventing worsening of microalbuminuria than metoprolol in hypertensive patients with the metabolic syndrome\(^{195}\); carvedilol also improved insulin sensitivity and glycemic control\(^{196}\). Nebivolol, another \(-\)blocker with vasodilating properties, is also useful in the treatment of hypertensive patients with CV risk factors\(^{197}\); it has no effect on insulin sensitivity\(^{198,199}\).

Among the newer drugs, moxonidine, a centrally active imidazoline-1 receptor agonist, effectively lowers BP and has a beneficial effect on lipid and carbohydrate metabolism\(^{200}\). Moxonidine, as an add-on drug, caused a significant reduction in BP in elderly hypertensives who were poorly controlled with two or more antihypertensive agents\(^{201}\). Moxonidine is also being used as an add-on drug to ramipril (MA-\text{RIAGE} study) in hypertensive patients\(^{202}\), and ramipril or eprosartan and hydrochlorothiazide in diabetic patients with severe hypertension\(^{203}\). Rilmenidine, a selective imidazoline I\(_1\) receptor agonist is an effective antihypertensive agent, which improves glucose utilization and reduces microalbuminuria\(^{204,205}\).

Most patients eventually require two or more antihypertensive drugs to reach BP goal\(^{1,160,206}\). It is recommended that therapy in patients whose BP is more than 20/10 mm Hg above target at diagnosis be initiated with a combination of antihypertensive drugs\(^{1,206}\). The combinations may be given as individual prescriptions or as fixed-dose formulations\(^{206}\). Treatment with fixed-dose combinations, such as irbesartan + hydrochlorothiazide has provided with good BP control in more than two-thirds of hypertensive patients (of different ethnic groups) with the metabolic syndrome in the Irbesartan/HCTZ Blood Pressure Reductions in Di verse Patient Populations (INCLUSIVE)\(^{207,208}\). Lipid and BP targets were reached in a high % of hypertensive patients with coronary heart disease treated with a combination of amlodipine + atorvastatin\(^{209,212}\).

In conclusion, the recommendations for treatment of hypertensive patients with the metabolic syndrome are that each metabolic abnormality should be treated along with hypertension to provide CV, cerebrovascular and renal protection. The ACE inhibitors or ARBs are the drugs of choice, unless contraindicated. Diuretics (at low dose), calcium channel blockers have been used effectively, and that \(-\)blockers can be used in certain cases. Fixed drug combination may also be quite useful.

### References


39. Cameron AJ, Shaw JE, Zimmet PZ. The metabolic syndrome: prevalence in worldwide populations. Endo-


69. Cheal KL, Abbasi F, Lamendola C, McLaughlin T, Reaven GM, Ford ES. Relationship to Insulin Resistan-


75. MAison P, Byrne CD, Hales CN, Day NE, Wareham NJ. Do different dimensions of the metabolic syndrome change together over time? Evidence supporting obesity as the central feature. Diabetes Care 2001;24:1758-1763.


134. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients - RIO-North America: A randomized controlled trial. JAMA 2006;295:761-775.


