Metabolic Syndrome and Cardiovascular Risk in Primary Hypertension

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The metabolic syndrome can be found in approximately one third of patients who do not have diabetes but have primary hypertension. Its presence has been associated with a wide range of traditional and nontraditional cardiovascular risk factors and early signs of cardiovascular and renal damage. Moreover, it was emphasized recently that the metabolic syndrome predicts an increased probability of sustaining a cardiovascular event or dying. In the clinical setting of insulin resistance, attention should be paid to the metabolic side effects of antihypertensive drugs; therefore, preference should be given to renin-angiotensin system inhibitors and calcium channel blockers rather than to β blockers and diuretics.


Metabolic syndrome is characterized by the simultaneous occurrence of several metabolic and nonmetabolic abnormalities that result in a marked increase in cardiovascular morbidity and mortality. The awareness and interest of the cardiovascular community in the metabolic syndrome arose in 1988, when Reaven (1) observed how dyslipidemia, hypertension, and hyperglycemia tended to cluster in some individuals. He called this clustering “syndrome X” and emphasized its role as a risk factor for cardiovascular disease. Because the main pathophysiologic feature underlying this condition is the presence of peripheral tissue resistance to insulin action, the syndrome also commonly is referred to as “insulin resistance syndrome.”

A number of scientific agencies have proposed several working definitions for the metabolic syndrome (2–5). The definition by Adult Treatment Panel III is perhaps the most physician friendly because it does not require direct assessment of insulin resistance and therefore is easier to apply in clinical practice.

Recent large epidemiologic surveys indicate that the age-adjusted prevalence of the metabolic syndrome is 24% in the United States (6), a figure that is rising rapidly, mainly because of the continuous increase in the prevalence of obesity (7). As a result of the high incidence of diabetes and cardiovascular complications associated with the metabolic syndrome, this condition has a remarkable impact on clinical practice, and its costs, direct and indirect, draw a significant share of public health resources.

BP levels are strongly associated with insulin levels and the degree of insulin resistance (8). It has been reported that insulin resistance might be involved in the pathogenesis of primary hypertension in up to 40 to 50% of cases. In the clinical setting of insulin resistance, hypertension may arise from the interactions of several mechanisms, such as increased renal sodium reabsorption, increased sympathetic neural outflow, and impaired ability of insulin to dilate the peripheral vasculature (9). Indeed, high BP is a classical feature of the metabolic syndrome, and it has been reported that the metabolic syndrome is present in up to one third of hypertensive patients (10,11).

Metabolic Syndrome and Cardiovascular Risk Factors

A wide range of traditional and nontraditional cardiovascular risk factors that may promote and foster the development of atherosclerosis have been reported in association with the metabolic syndrome, including atherogenic dyslipidemia, prothrombotic and proinflammatory milieu, and endothelial dysfunction. Patients with the metabolic syndrome often show elevated small and dense LDL cholesterol particles and elevated levels of apolipoprotein B (12). Small, dense LDL particles are more atherogenic than the large ones, and apolipoprotein B-100 is the major apolipoprotein component of the atherogenic lipoproteins (VLDL, LDL, and intermediate density lipoprotein) (13). Increased levels of clotting factors (tissue factor VII and fibrinogen), inhibition of the fibrinolytic pathway (increased plasminogen activator inhibitor-1 and decreased tissue plasminogen activator activity), and increased platelet aggregability also have been described in the metabolic syndrome, which therefore can be considered a prothrombotic condition (14). Furthermore, the metabolic syndrome signals the presence of a proinflammatory state. In fact, increased C reactive protein levels often can be found in patients with the metabolic syndrome, and there is a linear relationship between the number of components of the metabolic syndrome and the degree of inflammation (15). An impairment in endothelial

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function, as indicated by a higher transcapillary escape rate of albumin and defective forearm response to acetylcholine, also has been described in untreated hypertensive patients who did not have diabetes but had the metabolic syndrome without overt cardiovascular disease (16). These abnormalities contribute to the development of asymptomatic structural and functional abnormalities at the vascular and cardiac levels and may lead to the onset of major cardiovascular events.

**Metabolic Syndrome and Target Organ Damage**

Several studies have shown a significant, independent association between the metabolic syndrome and subclinical cardiovascular and renal damage both in the general population and in patients with primary hypertension. We and others have described an association between the metabolic syndrome and greater left ventricular mass index and prevalence of left ventricular hypertrophy, especially concentric hypertrophy, in patients with primary hypertension (10,17). Moreover, in a group of 354 untreated hypertensive patients without diabetes, we found a linear relationship between the number of components of the metabolic syndrome and the prevalence and the degree of left ventricular hypertrophy. We also showed that the presence of the metabolic syndrome entails a twofold increased risk for left ventricular hypertrophy, even after adjustment for several potentially confounding variables (17). Furthermore, in a large group of patients with primary hypertension, we reported that the metabolic syndrome is a significant, independent predictor of carotid atherosclerosis (17), thus extending previously reported, similar results in the general population (18–20). The relationship between the metabolic syndrome and increased urinary albumin excretion is so strong that microalbuminuria has been taken as a criterion to define the occurrence of the metabolic syndrome (3). Cuspidi et al. (10) reported that higher urinary albumin excretion and prevalence of microalbuminuria were associated with the occurrence of the metabolic syndrome in a group of 447 hypertensive patients. More recently, we showed that the metabolic syndrome is a significant, independent predictor of the presence of microalbuminuria in a large group of untreated patients with primary hypertension. Moreover, we found a linear relationship between the number of components of the metabolic syndrome and the prevalence and the degree of microalbuminuria (17). In the general population, the metabolic syndrome has been related to higher serum creatinine and urinary albumin excretion and lower GFR: the greater the number of components of the metabolic syndrome and the prevalence of chronic kidney disease and microalbuminuria. Furthermore, the risk for chronic kidney disease and microalbuminuria increases as the number of components of the metabolic syndrome increases and is 2.6- and 1.9-fold higher, respectively, in the presence of the metabolic syndrome (21).

**Prognostic and Therapeutic Implications**

There is now a large body of evidence showing that the metabolic syndrome predisposes individuals to the development of cardiovascular disease. For example, an analysis of 3606 individuals with a family history of type 2 diabetes demonstrated that those with the metabolic syndrome showed a significant increase in cardiovascular mortality (22). Similarly, in a large group of middle-aged Finnish men over a mean follow-up of 11.6 yr, the presence of the metabolic syndrome predicted all-cause and cardiovascular mortality even in the absence of cardiovascular disease and diabetes at baseline (23). The Second National Health and Nutrition Examination Survey showed that patients with the metabolic syndrome had a higher risk for cardiovascular death, coronary heart disease, and stroke. Furthermore, the higher the number of the metabolic syndrome criteria, the higher the incidence of mortality as a result of cardiovascular disease (24). More recently, an analysis of data from the Atherosclerosis Risk in Communities Study showed that individuals who have the metabolic syndrome without diabetes or cardiovascular disease are at increased risk for long-term, poor cardiovascular outcome (25).

Both the Seventh Report of the Joint National Committee (26) and the European Society of Hypertension–European Society of Cardiology Guidelines (27) emphasize the importance of diagnosing the metabolic syndrome when treating hypertensive patients. The Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study, which included 1742 initially untreated essential hypertensive patients without cardiovascular disease, recently showed that the metabolic syndrome amplifies the risk associated with high BP, independent of several traditional cardiovascular risk factors. Actually, over a mean follow-up period of 4.1 yr, the presence of the metabolic syndrome was a significant independent predictor of both cardiac (hazard ratio 1.5) and cerebrovascular (hazard ratio 2.1) events. The adverse prognostic value of the metabolic syndrome was attenuated but still significant among hypertensive patients without diabetes (11).

Recognizing the metabolic syndrome in patients with hypertension provides a great opportunity for more aggressive treatment, including lifestyle modification and treatment of comorbidity factors so as to attain cardiovascular risk reduction. Most of the cardiovascular risk reduction that is associated with antihypertensive drugs is the result of BP lowering alone; however, in the clinical setting of insulin resistance, consideration should be given to the metabolic side effects of antihypertensive drugs. Therefore, drugs that inhibit the renin-angiotensin system, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, should be preferred because of their proven protective effect on the incidence of new-onset diabetes. Calcium channel blockers are neutral from a metabolic standpoint and could be useful both as first-line and as add-on treatment. β Blockers and diuretics are less attractive in the context of insulin resistance because they are known to worsen metabolic abnormalities, even though they often are necessary to achieve BP goals.

**References**

2. Expert Panel on Detection, Evaluation, and Treatment of


