

HYPERTENSION AND THE METABOLIC SYNDROME

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SUMMARY

Hypertension is a very common condition which frequently remains undiagnosed until relatively late in its course, leading to a variety of other life-threatening conditions like kidney damage and heart failure. It is a very prominent feature of the metabolic syndrome, present in up to 85% of patients. In the context of global cardiovascular risk, metabolic syndrome is indeed a high risk condition, involving obesity, dyslipidemia, hypertension and diabetes. In spite of controversy surrounding its definition and etiology, metabolic syndrome represents a useful and simple clinical concept which allows for earlier detection of type 2 diabetes and cardiovascular disease. The establishment of hypertension as a component of the syndrome has enabled better insight into the condition and allowed for earlier detection and treatment. Hypertension is associated with the laboratory and anthropometric findings linked to the metabolic syndrome. Insulin resistance and central obesity, recognized as the main factors involved in the

pathophysiology of the metabolic syndrome, contribute to elevated blood pressure, which further promotes vascular damage in cardiac, renal, and brain tissue. Insulin resistance and the resulting hyperinsulinemia induce blood pressure elevation by the activation of sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) with consequential sodium retention and volume expansion, endothelial dysfunction and alteration in renal function. Visceral fat, in comparison to subcutaneous tissue, represents a metabolically active organ, strongly related to insulin sensitivity. Moderating the secretion of various adipocytokines like leptin, adiponectin, plasminogen activator inhibitor 1 (PAI-1), tumor necrosis factor alfa (TNF- α), interleukin-6 (IL-6) and resistin, it is associated with the processes of inflammation, endothelial dysfunction, hypertension and atherogenesis. One of the proposed mechanisms by which hypertension is linked with central obesity includes sympathetic nervous system overactivation. Therapeutic approach to patients with hypertension and metabolic syndrome includes modification of unhealthy lifestyle that aggravates the underlying pathology. This treatment includes sodium restriction, alcohol and calorie restriction, smoking cessation, weight reduction, and increased physical activity. However, it is often not sufficient to obtain the target values of blood pressure, especially in patients with

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type 2 diabetes. Concerning pharmacological agents, emphasis is in particular placed on the RAAS blockade with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, and on central sympatholytic agents that exert additional beneficial effects.

The overall importance of arterial hypertension relies on two facts. It is a very common condition in clinical practice, one of the most important risk factors in the development of cardiovascular disease, and the leading cause of morbidity and mortality in the modern world. Hypertension frequently remains undiagnosed until relatively late in its course, leading to a variety of other life-threatening conditions like kidney damage and heart failure (1,2).

The association of elevated blood pressure and metabolic abnormalities with poor cerebrovascular outcome had been recognized long before the concept of the metabolic syndrome became popular (3). However, until 1997, hypertension was defined as blood pressure value above 160/90 mmHg. Over the last decade, extensive randomized trials documenting that an increase in systolic or diastolic blood pressure of 5 mm Hg was associated with a concomitant increase in cardiovascular disease by 20%-30% have led to a revision of the definition of hypertension (4). For the first time, in 1997, the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (JNC VI) recommended a cut-off value of 140/90 mm Hg for the general population and 130/85 mm Hg for diabetic patients (5). JNC VII recommended a value of 130/80 mm Hg for diabetic patients in 2003 (6). In the same year, the European Society of Hypertension and Cardiology (ESH/ESC) recommended a new classification defining optimal blood pressure as a value under 120/80 mm Hg (7). They emphasized that there was no single value dividing normotension from hypertension. The threshold for the initiation of blood pressure treatment should be determined on the basis of global cardiovascular risk (associated risk factors, risk of future organ damage and target blood pressure values). Current guidelines suggest that the target for blood pressure lowering in diabetic patients is below that for the general population, at 130/80 mm Hg, or

lower in the presence of nephropathy. Antihypertensive therapy could be introduced in diabetic patients with high-normal blood pressure (1). Unfortunately, blood pressure goals stated in the current guidelines are difficult to achieve in clinical practice (Table 1).

Table 1. Blood pressure classification *ESH/ESC

Optimal	<120	<80 mmHg
Normal	120 – 129	80 – 84
High normal	130 – 139	85 – 89
Hypertension		
Stage I	140 – 159	90 – 99
Stage II	160 – 179	100 – 109
Stage III	≥ 180	≥ 110
Isolated systolic	≥ 140	< 90

* ESH/ESC: European Society of Hypertension/European Society of Cardiology
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However, the establishment of hypertension as a component of the metabolic syndrome, previously named syndrome X, has enabled better insight into the condition and allowed for earlier detection and treatment. In the context of global cardiovascular risk, metabolic syndrome is indeed a high risk condition, involving three or more risk factors, often organ damage and diabetes (1,8). The metabolic syndrome refers to the clustering of cardiovascular risk factors that include diabetes, obesity, dyslipidemia and hypertension. The incidence of the metabolic syndrome, which represents the most threatening epidemic in industrialized countries, is rapidly rising. Approximately 1 adult in 4 or 5, depending on the country, shows features of the syndrome. In the category over 50 years of age, it affects more than 40% of the population in the United States and nearly 30% in Europe (8). According to the World Health Organization (WHO) definition from 1999, the metabolic syndrome is present in a person with diabetes, impaired fasting glucose, impaired glucose tolerance or insulin resistance harboring at least two of the following criteria: waist-hip ratio >0.90 cm in men or >0.85 cm in women, serum triglycerides ≥150 mg/dL or HDL-C <35 mg/dL in men and <39 mg/dL in women, urinary albumin excretion rate >20 mcg/min and blood pressure ≥140/90 mm Hg (9).

In 2001, the National Cholesterol Education Program – Adult Treatment Panel (NCEP –ATP III) defined the metabolic syndrome as having at least three of the following abnormalities: waist circumference >102 cm in men and >88 cm in women, serum triglycerides ≥ 150 mg/dL, HDL-C <40 mg/dL in men and <50 mg/dL in women, blood pressure $\geq 130/85$ mm Hg, and serum glucose ≥ 110 mg/dL (10). In 2005, the International Diabetes Federation (IDF) proposed a modified definition based on clinical criteria and designed for global application in clinical practice. This definition represents modifications of the WHO and ATP III definitions and has greater emphasis on visceral obesity as the core feature of the syndrome (11). Visceral obesity measured by waist circumference is an essential requirement for the diagnosis, while other variables employed by ATP III are slightly modified (Table 2). IDF defined visceral

Table 2. **IDF definition of the metabolic syndrome**

- Central obesity (waist circumference)
- in Caucasian >94 cm in men, >80 cm in women,
- +
- At least 2 of the following:
 - triglycerides >1.7 mM or specific treatment for lipid abnormality
 - HDL-cholesterol <0.9 mM in men, <1.1 mM in women or specific treatment for lipid abnormality
- RR >130 systolic or >85 mm Hg diastolic or treatment of previously diagnosed hypertension
- Fasting glucose >5.6 mM or previously diagnosed type 2 diabetes or IGT

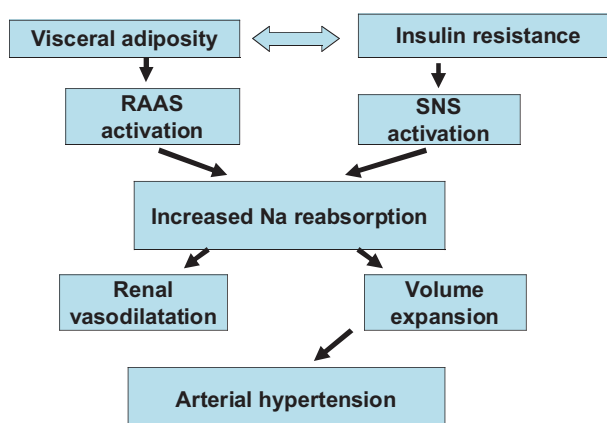
obesity for different ethnic populations based on waist circumference measurements obtained from epidemiologic data on various ethnic populations (11). As the precise pathophysiology is unknown, the metabolic syndrome is still the source of medical controversy. Recently, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have advised refocusing on the individual components of the syndrome without regarding the syndrome as an identifiable target. This statement has not been accepted by the IDF, which emphasizes that whatever the uncertainties of definition and etiology, it is advisable to consider metabolic syndrome as a whole.

This syndrome represents a useful and simple clinical concept which allows for earlier detection of type 2 diabetes and cardiovascular disease (12,13).

In spite of a recent debate and controversy surrounding the definition and etiology of the syndrome, there is no doubt that hypertension is associated with the laboratory and anthropometric findings linked to type 2 diabetes and metabolic syndrome (14). In fact, hypertension affects up to 85% of patients with metabolic syndrome. On the other hand, patients with metabolic syndrome have a 5.5-fold risk of diabetes and 2-fold risk of new hypertension recorded in patients without this syndrome (15).

Moreover, studying hypertension in the context of the metabolic syndrome has provided significant insights into the etiology of the condition, known to be complex and multifactorial (16-18). Although the cause of hypertension in the metabolic syndrome has not been completely understood, insulin resistance and central obesity have been recognized as the main factors involved in its pathophysiology (Figure 1).

Figure 1. **Pathogenesis of hypertension in the metabolic syndrome**



Multiple studies were performed in order to elucidate the mechanisms of this association. These studies have shown that all of the elements of the syndrome contribute to increased blood pressure, which further promotes vascular damage in cardiac, renal and brain tissue (14,16). Insulin resistance could be defined as the inability of insulin to produce its numerous

actions, in spite of unimpaired secretion from beta cells. It could be caused by various genetic and acquired conditions (16).

Except for a few rare cases involving antibodies against insulin receptor or mutations in the insulin receptor gene, insulin resistance of the metabolic syndrome results from impairments in cellular events distal to the interaction between insulin and its surface receptor (19,20). Metabolic abnormalities result from the interaction between the effects of insulin resistance located primarily in muscle and adipose tissue and the adverse impact of the compensatory hyperinsulinemia on tissues that remain normally insulin sensitive (16,19,20).

Insulin resistance and the resulting hyperinsulinemia induce blood pressure elevation by activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) with consequential sodium retention and volume expansion, endothelial dysfunction and alteration in renal function (17,20,21). Hyperinsulinemia stimulates the activation of RAAS in blood vessels and the heart, generating the production of angiotensin II and its pro-atherogenic effects. At the same time, hyperinsulinemia in insulin resistant subjects stimulates the mitogen-activated protein kinase (MAPK) pathway, which promotes vascular and cardiac injury (16,17). The local RAAS in the visceral adipose tissue exerts more powerful systemic effects compared with the subcutaneous adipose tissue. Angiotensin II acts through angiotensin 1 receptors, inhibiting the vasodilatory effects of insulin on blood vessels and glucose uptake into the skeletal muscle cells by blocking insulin action on phosphatidylinositol-3 kinase and protein kinase beta through free oxygen production (16,20). This leads to a decrease in nitric oxide (NO) production in endothelial cells and vasoconstriction in smooth muscle cells, and inhibits glucose transport (GLUT 4) in skeletal muscles. The other mechanism by which insulin resistance contributes to hypertension includes the overactivity of angiotensin 1 receptor, which further leads to vasoconstriction and volume expansion (19-21). Although adiposity has been traditionally defined as an increase in total body mass, cardiovascular risk is associated with visceral fat

accumulation (22). Increased visceral fat accumulation is a strong predictor of arterial hypertension. One of the proposed mechanisms by which hypertension is linked with central obesity includes sympathetic nervous system overactivation (23-26). Chronic sympathetic stimulation facilitates energy balance and weight stabilization in chronic overeating, but at the cost of adverse consequences such as elevated blood pressure. It has also been suggested that chronic increases in portal venous fatty acid levels may be responsible for hypertension that accompanies visceral obesity. Increases in portal venous fatty acid concentrations have significant pressor effects, perhaps mediated by increased sympathetic tone (23,24). Visceral fat, in comparison to subcutaneous tissue, represents a metabolically active organ, strongly related to insulin sensitivity (22). Moderating the secretion of various adipocytokines like leptin, adiponectin, plasminogen activator inhibitor 1 (PAI-1), tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6) and resistin, it is associated with the processes of inflammation, endothelial dysfunction, progression of hypertension and atherogenesis. Visceral adipose tissue is a production depot for cytokines including TNF- α , which stimulates IL-6 production, and further generates the production of C-reactive protein (CRP), fibrinogen and PAI-1 resulting in a pro-thrombotic state. Circulating levels of these cytokines are generally increased in obese subjects and in patients with diabetes (23,24).

On the contrary, visceral adiposity is a state with a relative deficiency of adiponectin, the adipocyte “good guy”, which increases insulin sensitivity, glucose uptake in muscle cells and free fatty acid oxidation. This cytokine exerts antidiabetic, anti-inflammatory and antiatherogenic effects. Many studies have shown increased plasma adiponectin values in patients with hypertension as compared to normotensive population, as well as a negative correlation between adiponectin and mean systolic and diastolic blood pressure values. For those reasons, adiponectin was proposed as a marker of arterial hypertension (22-24).

Therapeutic approach to patients with hypertension and metabolic syndrome includes non-pharmacological therapy, as it is important to modify

unhealthy lifestyle that aggravates the underlying pathology. This treatment includes sodium restriction, alcohol and calorie restriction, smoking cessation, weight reduction, and increased physical activity. However, it is often not sufficient to obtain the target values (27,28). This fact underlines the therapeutic importance of pharmacological interventions capable of reducing blood pressure and other abnormalities related to metabolic syndrome like dyslipidemia, obesity and diabetes. Among pharmacological agents, particular emphasis is placed on the RAAS blockade with ACE inhibitors and angiotensin II receptor blockers, and central sympatholytic agents that exert additional beneficial effects (29,30). Evidence has been provided that drugs acting on the renin-angiotensin system should be the drugs of choice considering their sympathetic inhibitory effect and increase in insulin sensitivity (28). Central sympatholytic agents, particularly I1 imidazoline drugs, are also indicated, given their favorable metabolic effects. Drugs of the imidazoline (I1) class inhibit sympathetic nervous system outflow from the brain, counteracting one of the pathophysiological

abnormalities in hypertensive patients with metabolic syndrome, i.e. activation of the sympathetic nervous system. Inhibition of the sympathetic outflow to skeletal muscle blood vessels further exerts the beneficial effect of increasing insulin sensitivity (31). Patients with metabolic syndrome require strict blood pressure control. If type 2 diabetes is present, in 2/3 of them target blood pressure values could be achieved only with two or more antihypertensive drugs (14,28).

In conclusion, hypertension is more than just elevated blood pressure, it is intimately associated with the metabolic syndrome. The frequent association between hypertension and multiple risk factors for cardiovascular disease is more than a chance finding (32). In patients with metabolic syndrome a multi-target approach based on the assessment of the overall cardiovascular risk should be applied. Increased understanding of the mechanisms contributing to hypertension in the metabolic syndrome, as well as critical analysis of the results of antihypertensive trials in patients with diabetes are important to develop a logical, evidence-based treatment strategy.

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