

8. HYPERTENSION AND THE METABOLIC SYNDROME

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The overall importance of arterial hypertension relies on two facts. It is a very common condition in clinical practice and one of the most important risk factors in the development of cardiovascular disease, 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.

The association of increased blood pressure and metabolic abnormalities with poor cerebrovascular outcome had been recognized long before the concept of the metabolic syndrome became popular.

However, until 1997, hypertension was defined as blood pressure value above 160/90mmHg. Over the last decade extensive randomized trials documenting that an increase in systolic or diastolic blood pressure of 5mmHg was associated with a concomitant increase in cardiovascular disease of 20-30%, have led to a revision of the definition of hypertension. 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 140/90mmHg for the general population and 130/85mmHg for diabetic patients. JNS VII recommended a value of 130/80mmHg for diabetic patients in 2003. That same year, The European Society of Hypertension and Cardiology (ESH/ESC) recommended a new classification, defining an optimal blood pressure as a value under 120/80mmHg (Table 8.1.). 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)!

Table 8.1. Blood pressure classification *ESH/ESC

optimal	<120	<80 mmHg
normal	120 – 129	80 – 84
high normal	130 – 139	85 – 89
hipertension		
mild	140 – 159	90 – 99
moderate	160 – 179	100 – 109
severe	≥ 180	≥110
Izolated	≥ 140	≥ 90

*ESH/ESC: European Society of Hypertension/European Society of Cardiology
(From: Journal of Hypertension 2003,21:1011-53.)

Current guidelines suggest that the target for blood pressure lowering in diabetic patients is below that for the general population, at 130/80mmHg, or lower in the presence of

nephropathy (Table 8.2.) Unfortunately, blood pressure goals stated in the current guidelines are difficult to achieve in clinical practice.

Table 8.2. Guideline recommendations for BP goals

ESH/ESC* and JNC 7** recommend the following BP goals:
<140/90mmHg for essential hypertension
<130/80mmHg for hypertensive patients with diabetes
<125/75mmHg for hypertension with chronic kidney disease

*ESH/ESC: European Society of Hypertension/European Society of Cardiology

**JNC 7: Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 7th report

(From: Guidelines Committee. *J Hypertens* 2003; 21: 1011-53., Chobanian AV, *et al.* *JAMA* 2003; 289: 2560-72.)

However, the establishment of hypertension as a component of the metabolic syndrome, previously named syndrome X, has enabled more insight into the condition and allowed 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.

The metabolic syndrome refers to the clustering of cardiovascular risk factors that include diabetes, obesity, dyslipidemia and hypertension. 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 in men or > 0.85 cm in women, serum triglyceride \geq 150mg/dl or HDL-C < 35mg/dl in men and < 39mg/dl in women, urinary albumin excretion rate > 20 mcg/min and blood pressure \geq 140/90mmHg

In 2001, the National Cholesterol Education Program- Adult treatment panel (NCEP –ATPIII) 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 triglyceride \geq 150mg/dl, HDL-C < 40mg/dl in men and < 50mg/dl in women, BP \geq 130/85mmHg and serum glucose \geq 110mg/dl.

Last year, the International Diabetes Federation (IDF) has proposed a modified definition, which includes the presence of visceral obesity and at least two of the following criteria: triglyceride > 1.7 mM, HDL -C <0.9 mM in men and <1.1mM in women, systolic blood pressure > 130 or diastolic >85mmHg or taking medication for hypertension and glucose > 5.6 mM or a diagnosed diabetes.

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) advised refocusing on the individual components of the syndrome without regarding the syndrome as an identifiable target. This statement was not accepted by the International Diabetes Federation (IDF), which emphasized

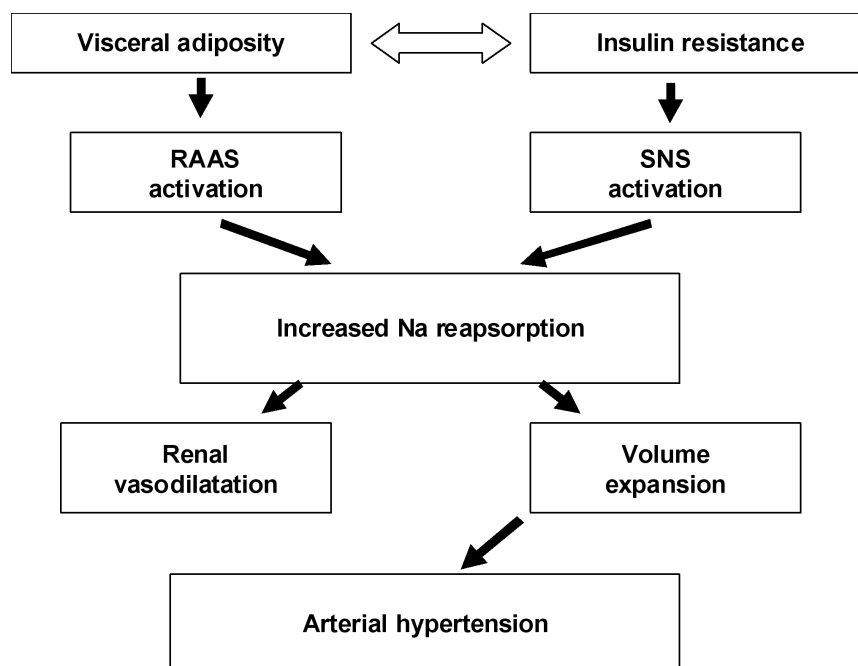
that whatever the uncertainties of definition and etiology, it is advisable to regard metabolic syndrome as a whole.

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 the metabolic syndrome. In fact, hypertension affects up to 80% of patients with type 2 diabetes and 40% of patients with metabolic syndrome. On the other side, patients with metabolic syndrome have a 5.5-fold higher risk of diabetes and a 2-fold higher risk of new hypertension compared with patients without metabolic syndrome.

Moreover, the study of hypertension in the context of the metabolic syndrome has provided significant insights into the etiology of the condition, known to be complex and multifactorial.

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 8.1.). 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.

Figure 8.1. Pathogenesis of hypertension in the metabolic syndrome



Insulin resistance could be defined as the inability of insulin to produce its numerous actions, in spite of unimpaired secretion from the beta cells. It could be caused by various genetic and acquired conditions.

Except in 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. 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.

Insulin resistance and the resulting hyperinsulinemia induce blood pressure elevation by activation of sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) with a consequential sodium retention and volume expansion, endothelial dysfunction and alteration in renal function. 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. 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. 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 second mechanism by which insulin resistance contributes to hypertension includes the overactivity of angiotensin 1 receptor which further leads to vasoconstriction and volume expansion.

Endothelial dysfunction is present early in the state of insulin resistance, even before other components of the metabolic syndrome appear.

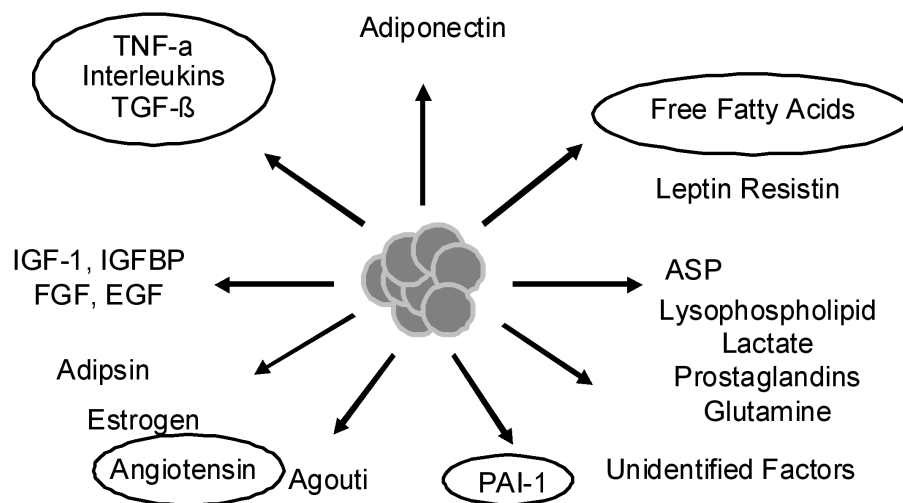
Although adiposity has been traditionally defined as an increase in total body mass, cardiovascular risk is associated with visceral fat accumulation. Increased visceral fat accumulation is a strong predictor of arterial hypertension. One of the proposed mechanisms by which hypertension is linked with central obesity includes sympathetic nervous system overactivation. 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.

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 alpha (TNF- α), interleukin-6 (IL-6), resistin, it is associated with the processes of inflammation, endothelial dysfunction, progression of hypertension and atherogenesis (Figure 8.2.).

Visceral adipose tissue is a production depot for cytokines including TNF α , which stimulates IL-6 production, and further generates production of C-reactive protein (CRP), fibrinogen and PAI-1 resulting in pro-thrombotic state. Circulating levels of these cytokines are generally increased in obese subjects and in patients with diabetes.

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 anti-diabetic, anti-inflammatory and anti-atherogenic 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.

Figure 8.2. The relationship between visceral adipose tissue and cardiovascular disease



Therapeutic approach to patients with hypertension and metabolic syndrome include non-pharmacological therapy, as it is important to change the unhealthy lifestyle which aggravates the underlying pathology. This treatment includes sodium restriction, alcohol and calorie restriction, smoking cessation, weight reduction, increased physical activity. However, it is often not sufficient to obtain the target values. Between pharmacological agents, a particular emphasis is placed on the RAAS blockade with ACE inhibitors and angiotensin II receptor blockers, which exert additional beneficial effects.

Patients with metabolic syndrome require strict blood pressure control, which could be achieved in 2/3 of patients only with two or more antihypertensive drugs.

In summary, 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. In patients with metabolic syndrome a multitarget 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 is important to develop a logical, evidence-based treatment strategy.

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