The metabolic syndrome in hypertension: European society of hypertension position statement

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The metabolic syndrome considerably increases the risk of cardiovascular and renal events in hypertension. It has been associated with a wide range of classical and new cardiovascular risk factors as well as with early signs of subclinical cardiovascular and renal damage. Obesity and insulin resistance, beside a constellation of independent factors, which include molecules of hepatic, vascular, and immunologic origin with proinflammatory properties, have been implicated in the pathogenesis. The close relationships among the different components of the syndrome and their associated disturbances make it difficult to understand what the underlying causes and consequences are. At each of these key points, insulin resistance and obesity/proinflammatory molecules, interaction of demographics, lifestyle, genetic factors, and environmental fetal programming results in the final phenotype. High prevalence of end-organ damage and poor prognosis has been demonstrated in a large number of cross-sectional and a few number of prospective studies. The objective of treatment is both to reduce the high risk of a cardiovascular or a renal event and to prevent the much greater chance that metabolic syndrome patients have to develop type 2 diabetes or hypertension. Treatment consists in the opposition to the underlying mechanisms of the metabolic syndrome, adopting lifestyle interventions that effectively reduce visceral obesity with or without the use of drugs that oppose the development of insulin resistance or body weight gain. Treatment of the individual components of the syndrome is also necessary. Concerning blood pressure control, it should be based on lifestyle changes, diet, and physical exercise, which allows for weight reduction and improves muscular blood flow. When antihypertensive drugs are necessary, angiotensin-converting enzyme inhibitors, angiotensin II-AT1 receptor blockers, or even calcium channel blockers are preferable over diuretics and classical β-blockers in monotherapy, if no compelling indications are present for its use. If a combination of drugs is required, low-dose diuretics can be used. A combination of thiazide diuretics and β-blockers should be avoided. *J Hypertens* **26:1891–1900 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Abbreviations: ACE, Angiotensin-Converting Enzyme; ACEi, Angiotensin-Converting Enzyme inhibitors; ARA II, Angiotensin II-AT1 Receptor blockers; ARB, Angiotensin II-AT1 Receptor Blockers; ARB, Angiotensin Receptor Blocker; ATP III, Adult Treatment Panel III; CB_1 receptor blockers, Cannabinoid type 1 Receptor Blockers; CB_1, Cannabinoid type 1; CCB, Calcium-Channel Blocker; CPR, C-Reactive Protein; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; EGIR, European Group of Insulin Resistance; EKG, Eelektrokardiogramm; ELSA, European Lacidipine Study on Atherosclerosis; FFA, Free Fatty Acid; GFR, Glomerular Filtration Rate; HDL, High-Density Lipoprotein; IDF, International Diabetes Federation; IFG, Impairing Fasting Glucose; IMT, Intima-Media Thickness; LDL, Low-Density Lipoprotein; LVH, Left Ventricular Hypertrophy; MDRD, Modification of Diet in Renal Disease; NHANES III, National Health and Nutrition Examination Survey III; NHBLI, National Heart Blood and Lung Institute; PAMELA, Pressioni Arteriose Monitorate E Loro Associazioni; PPAR-γ, Proliferator-Activated Receptor-Gamma; PWV, Pulse Wave Velocity; STAR, The Study of Trandolapril/Verapamil SR and Insulin Resistance; VALUE, Valsartan Antihypertensive Long-term Use Evaluation

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Introduction

Arterial hypertension is often part of a constellation of anthropometric and metabolic abnormalities that include abdominal (or visceral) obesity, characteristic dyslipidemia (low high-density lipoprotein cholesterol and high triglycerides), glucose intolerance and insulin resistance, and hyperuricemia. These features occur simultaneously to a higher degree than would be expected by chance alone, supporting the existence of a discrete disorder, the so-called metabolic syndrome. The metabolic syndrome is currently considered to confer an increased risk of cardiovascular events attributable, in part, to the individual risk factors that concur in defining it and, in part, to a cluster of other factors such as hyperuricemia, a proinflammatory state, impaired fibrinolysis, and oxidative stress, which usually go along with it.

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The clinical significance of diagnosing the metabolic syndrome in an individual has been challenged recently. Some authors and scientific societies have claimed that the metabolic syndrome is not a single pathophysiological entity, that its identification has neither pedagogical nor clinical utility, and that clinical emphasis should rather be placed on effectively treating any cardiovascular risk factor that is present [1,2]. However, although the causes and mechanisms of the metabolic syndrome may indeed be diversified (which is what the term 'syndrome' implies), there is evidence that the overall cardiovascular risk accompanying this condition may be greater than the sum of its identifiable components [3]. Furthermore, these components are often defined by values that are lower than those meeting the definition of risk factors by many guidelines, which may thus fail to detect the presence of a high cardiovascular risk in several individuals with metabolic syndrome. Finally, the simple and easy identification of the metabolic syndrome favors the use of this approach in clinical practice, which resists use of the more complex charts for total cardiovascular risk quantification, ultimately helping implementation of cardiovascular prevention.

The metabolic syndrome is extremely common worldwide and can be found in approximately one-third of patients with essential hypertension in whom it considerably increases the risk of cardiovascular and renal events, even in the absence of overt diabetes. Its presence has been associated with a wide range of classical and also new cardiovascular risk factors as well as with early signs of subclinical cardiovascular and renal damage. In the present study, the prevalence, mechanisms, prognostic significance, and treatment of the metabolic syndrome in hypertensive patients are reviewed. Management recommendations are given and areas in need of future research and improved knowledge are recognized.

Definition

There is no universally accepted definition for the metabolic syndrome. Since the description by Reaven [1], many names have been given to various clusters of cardiovascular risk factors but, today, the most commonly used name are the metabolic syndrome or cardiometabolic syndrome. Similarly, the criteria employed to identify the metabolic syndrome have changed over the years [4–9] (Table 1). After the more mechanistic World Health Organization and European Group for Insulin Resistance definitions, the Adult Treatment Panel III (ATP III), one of the metabolic syndromes presented in 2001 [8,9], was more clinically oriented. More recently, the International Diabetes Federation definition [6] aims at considering research needs but also at offering an accessible diagnostic tool suitable for worldwide use. The most important new element, as compared to other definitions, is that, although the pathogenesis of the metabolic syndrome and the contribution of each of its components is complex and still not well understood, central obesity and insulin resistance are regarded as the most important causative factors. The last of the definitions was released by the American Heart Association/National Heart Blood and Lung Institute) (AHA/NHBLI) [8,9]. It has given support to the ATP III criteria, except for a reduction in the threshold of the impaired fasting glucose component from 6.1 to 5.6 mmol/l (110–100 mg/dl) in line with the recent modification proposed by the American Diabetes Association [10]. This lower cut-off point was not adopted in Europe and is not recommended by the WHO [11].

Mechanisms of hypertension in the metabolic syndrome

Mechanisms involved in the metabolic syndrome are obesity, insulin resistance and a constellation of independent factors, which include molecules of hepatic, vascular, and immunologic origin with proinflammatory properties. Although insulin resistance is associated with obesity and central adipose tissue, not all obese subjects have insulin resistance. Skeletal muscle and the liver, not adipose tissue, are the two key insulin-response tissues involved in maintaining glucose balance, although abnormal insulin action in the adipocytes also plays a role in development of the syndrome. At each of these key

Table 1 Criteria for diagnosing the metabolic syndrome according the different scientific organisms

Organisms	Principal criteria	Abdominal obesity	Glucose (mg/dl)	HDL (mg/dl)	TG (mg/dl)	BP (mmHg)
WHO [4]	DM, GI or IR	BMI $\geq$30 kg/m^2 M $\geq$0.90 W $\geq$0.85		M $\leq$ 35 W $\leq$ 39 (1.02 mmol/l)	$\geq$150 (1.7 mmol/l)	$\geq$140/90[a]
EGIR [5]	IR or FI >P75	BMI $\geq$30 kg/m^2 M $\geq$102 cm W $\geq$88 cm	$\geq$110[a] (6.1 mmol/l)	<40 (1.03 mmol/l)	$\geq$180	$\geq$140/90[a]
ATPIII [6]		M $\geq$102 cm W $\geq$88 cm	$\geq$110[a] (6.1 mmol/l)	M $\leq$ 40 (1.03 mmol/l) W $\leq$ 50 (1.29 mmol/l)	$\geq$150 (1.7 mmol/l)	$\geq$135/85[a]
IDF [7]	Central obesity	M $\geq$94 cm W $\geq$80 cm	$\geq$100[a] (5.6 mmol/l)	M $\leq$ 40 (1.03 mmol/l) W $\leq$ 50[a] (1.29 mmol/l)	$\geq$150[a] (1.7 mmol/l)	$\geq$135/85[a]
AHA [8,9]		M $\geq$94 cm W $\geq$80 cm	$\geq$100[a] (5.6 mmol/l)	M $\leq$ 40 (1.03 mmol/l) W $\leq$ 50[a] (1.29 mmol/l)	$\geq$150[a] (1.7 mmol/l)	$\geq$135/85[a]

Diagnosis of metabolic syndrome is based on: principal criteria plus at least two other; in those without principal criteria, at least three. Shaded area denotes the definitions based on carbohydrate metabolism abnormalities. The remaining are based on abdominal obesity. AHA, American Heart Association; ATP III, Adult Treatment Panel III; BP, blood pressure; DM, diabetes mellitus; EGIR, European Group for the Study of Insulin Resistance; FI, fasting insulin; GI, glucose intolerance; IDF, International Diabetes Federation; IR, insulin resistance; M, men; TG, triglycerides; W, women; WHO, World Health Organization. [a] Or in treatment for.

points, insulin resistance and obesity/proinflammatory molecules are interactions of demographics, lifestyle, genetic factors, and environmental fetal programming. Superimposing upon these are infections and/or chronic exposure to certain drugs that can also make their contribution. All interact to create the final individual phenotype [8,9,12–15]. Likewise, they interact leading to changes in the blood pressure (BP) regulatory mechanisms.

Hypertension is frequent in the metabolic syndrome, and more so is the BP abnormality, with values in the high normal range, that represents one of the five components that lead to the identification of this condition. In the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) population study, for example, a BP in the high normal or frankly hypertension range was found in more than 80% of individuals with the metabolic syndrome, followed in a decreasing order of prevalence by visceral obesity, lipid abnormalities, and impaired fasting glucose [16]. The high prevalence of BP abnormalities in the metabolic syndrome explains the very frequent occurrence of subclinical organ damage of the type that is frequently associated with and dependent on a BP elevation such as left ventricular hypertrophy (LVH), arterial stiffening and increased urinary protein excretion [16]. Some of these types of organ damage, however, show an increased prevalence also in individuals who have the metabolic syndrome without a BP elevation, suggesting that other components of this condition play a role independently of BP.

In general, the metabolic syndrome components are characterized by a high degree of interaction, one contributing to the establishment of the abnormality of the other and vice versa. It has been recognized for many years, for example, that two main components of the metabolic syndrome, obesity and insulin resistance, may play an important role in the increment of BP and the development of hypertension, although the precise mechanisms that are involved remain partially unresolved. Factors commonly associated with and partly dependent on obesity and insulin resistance, such as overactivity of the sympathetic [17,18], stimulation of the renin–angiotensin–aldosterone system [19], abnormal renal sodium handling [20], and endothelial dysfunction [21,22], need to be considered.

Table 2 Cross-sectional studies analyzing the association of the metabolic syndrome with hypertension-induced organ damage

References	Number of subjects (race)	Organ damage assessment	Diagnostic criteria for MS	Main result
LVH				
De Simone [26]	1627	Echocardiography	ATP III	Increases risk Related to the number of components
Cuspidi *et al.* [29]	447 (white)	Echocardiography	ATP III	Increases risk
Cuspidi *et al.* [27]	2500 (white)	Echocardiography	ATP III	Increases risk of large atrial size
Leoncini *et al.* [24]	354 (white)	Echocardiography	ATP III	Increases risk (twice risk) Related to the number of components
Mulè *et al.* [25]	353 (white)	Echocardiography	ATP III	Increases risk
Burchfiel *et al.* [28]	1572 (black)	Echocardiography	ATP III	Increases risk (twice) Related to the number of components
Mancia *et al.* [16]	2051 (white)[a]	Echocardiography	ATP III	Prevalence twice
Schillachi *et al.* [23]	618 (white)	Echocardiography	ATP III	Increases risk More in women (OR = 4.3) Related to the number of components
Navarro *et al.* [33]	8425 (white)	ECG	ATP III	Increases risk (OR = 1.43) Related to the number of components
Enlarged left atrial size				
Cuspidi *et al.* [29]	2500 (white)	Echocardiography	ATP III	Increases risk
Microalbuminuria				
Cuspidi *et al.* [29]	447 (white)	24-h urinary albumin excretion	ATP III	Increases risk
Leoncini *et al.* [24]	354 (white)	Albumin/creatinine ratio	ATP III	Increases risk (OR = 2.0) Related to the number of components
Mulè *et al.* [25]	353 (white)	24-h urinary albumin excretion	ATP III	Increases risk
Palaniappan *et al.* [30]	5659 (NHANES III)	Albumin/creatinine ratio	ATP III	Increases risk
Low glomerular filtration rate				
Navarro *et al.* [33]	8425 (white)	GFR $<60\,ml/min/1.73\,m^2$ MDRD formula	ATP III	Increases risk (OR = 1.43)
Carotid IMT				
Scutteri *et al.* [34]	471 (whites)	Carotid ultrasound		Increases risk (16%)
Kawamoto *et al.* [36]	1297 (Japanese)	Carotid ultrasound		IIncreases risk (OR = 1.56) Related to the number of components
Leoncini *et al.* [24]	354 (white)	Carotid ultrasound		Increases risk (OR = 2.0)
Zanchetti *et al.* [40]	2034 (white)	Carotid ultrasound	ATP III	Increased risk mean maximum IMT at common carotids and bifurcations
Vascular stiffness				
Scutteri *et al.* [34]	471 (BLSA)[b]	B-mode ultrasonography-derived calculation		Increases risk (32%)
Schillaci *et al.* [35]	162 (white)	Applanation tonometry		Increases risk

ATP III, Adult Treatment Panel III; GFR, glomerular filtration rate; IMT, intima-media thickness; LVH, left ventricular hypertrophy; MDRD, modification of diet in renal disease; MS, metabolic syndrome; NHANES III, National Health and Nutrition Examination Survey III; OR, odds ratio. [a] Population-based study. [b] Baltimore Longitudinal Study on Aging.

Metabolic syndrome and hypertension-induced organ damage

Cardiac

Several studies have demonstrated that the metabolic syndrome is associated with a high prevalence of LVH in hypertensive patients and that this is the case throughout a wide age spectrum (Table 2). Moreover, the number of metabolic syndrome components has been directly related to the risk of having electrocardiogram (EKG) [23] and echocardiographic LVH [24–26], although this has not been confirmed in other studies [27,28]. The effect of the metabolic syndrome on left ventricular structure has been reported to be more pronounced in women than in men, and shown to be partly independent of the effect of hemodynamic and nonhemodynamic determinants of left ventricular mass [29] including BP values over 24 h [16]. An analysis of the components of left ventricular mass has shown that posterior wall and interventricular septal thickness were significantly and independently associated with the number of metabolic syndrome components, in contrast with the left ventricular chamber size for which no such association was found [28]. Atrial enlargement, a prognostic factor for the development of atrial fibrillation and stroke, has also been associated with overweight, high fasting glucose and the metabolic syndrome, independently of left ventricular mass and geometry [27,29].

Renal

An increase in the prevalence of abnormal urinary albumin excretion has been observed among hypertensive patients with the metabolic syndrome, as compared to those without the metabolic syndrome [24,25,29,30], and indeed microalbuminuria has been considered a diagnostic element for the metabolic syndrome in early definitions of this condition (Table 2). The prevalence of microalbuminuria has been shown to increase with the number of metabolic syndrome components, a finding seen also in nondiabetic subjects [24]. Hyperinsulinemia, as an expression of insulin resistance, has been associated with microalbuminuria in hypertensive subjects [31,32].

The metabolic syndrome was also associated with lower glomerular filtration rate (GFR), as estimated using the modification of diet in renal disease formula, in a cross-sectional survey of hypertensive patients seen in primary care. Furthermore, the number of metabolic syndrome components was linearly related to the prevalence of GFR less than 60 ml/min/1.73 m^2 [33].

Large and small arteries

Evidence is available that aortic pulse wave velocity (PVW), a marker of aortic stiffness and an independent prognostic factor for cardiovascular morbidity and mortality, is higher in hypertensive patients with the metabolic syndrome, and an association of this condition with large artery stiffening has been found. It is associated with metabolic syndrome irrespective of age and the systolic BP value [34,35]. The metabolic syndrome has also been associated with a faster progression of aortic stiffness with age, independently of major individual cardiovascular risk factors [36], suggesting that it may promote premature vascular senescence. Not only aortic, but also carotid stiffness has been shown to increase with the number of metabolic syndrome components [37].

An association between metabolic syndrome and carotid intima-media thickness (IMT) has been observed in several studies [24,34,36,38–40] (Table 2), although to a weaker degree than that observed for markers of organ damage such as LVH and microalbuminuria, with the factors involved being not only hypertension, but also impairing fasting glucose (IFG), low-density lipoprotein-cholesterol, GFR, and smoking. In a large survey of Japanese subjects [36], it was found that the prevalence of carotid atherosclerosis increased progressively with the number of metabolic syndrome components in hypertensive patients but not in normotensive individuals.

Although data are available concerning small artery damage in patients with type 2 diabetes, reduced endothelium-dependent vasodilatation and inward hypertrophic remodeling [41] data on the effects of the components of metabolic syndrome on small arteries are lacking, despite the fact that microvascular dysfunction has been claim as an explanation for the associations among hypertension, obesity, and impaired-mediated glucose disposal [42].

Prognostic value of the metabolic syndrome in hypertension

A limited number of studies [16,43–46] have examined the prognostic importance of the metabolic syndrome and of its individual components in hypertension. The general characteristics and the main results of the studies are shown in Table 3. Overall, the presence of the metabolic syndrome was an independent predictor of cardiovascular events [44–46] or cardiovascular and all-cause mortality [16], even when the other cardiovascular risk factor were token in to account. Moreover, the risk increased with the number of metabolic syndrome components [46]. In contrast, in the European Lacidipine Study on Atherosclerosis (ELSA) study, a large cohort of well treated patients, outcomes were not different between metabolic syndrome and nonmetabolic syndrome patients, suggesting that effective antihypertensive treatment may largely counteract the obnoxious effects of metabolic syndrome [40].

The impact of metabolic syndrome in intermediate objectives such as PWV [47] or IMT [40] has been evaluated. While progression on PWV was significantly higher in subjects with the metabolic syndrome than in subjects with zero, one, or two factors, even after adjust-

Table 3 Follow-up studies on the impact of the metabolic syndrome in prognosis of hypertension

References	Number of subjects (race)	Outcome assessment (follow-up)	Diagnostic criteria for MS	Main result
Jepessen *et al.* [43]	2906 (white) population-based	Events-rate (8 years)	Fasting plasma triglycerides and HDL	Higher risk in subjects which combine hypertension and dyslipidemia
Schillaci *et al.* [44]	1742 (white) hypertensive patients	Cardiac and cerebrovascular events-rate (10.9 years)	ATP III	Twice risk for both cardiac and cerebral events
Onat *et al.* [45]	2225 (white) hypertensive patients	Cardiovascular morbidity and mortality (4.1 years)	Plasma triglycerides and HDL	Higher the risk in subjects with dyslipidemia
Dekker *et al.* [46]	1564 (white) Population-based	Cardiovascular morbidity and mortality (10 years)	ATP III, WHO, EGIR, ACE	Twice the risk
Mancia *et al.* [16]	2051 (white) population-based	All-cause death (148 months)	ATP III	Higher risk
Zanchetti *et al.* [40]	2034 (white)	Cardiovascular morbidity and mortality (4 years)	ATP III	No significant difference was found between patients with and without MS

ACE, angiotensin-converting enzyme; ATP III, Adult Treatment Panel III; EGIR, European Group of Insulin Resistance; HDL, high-density lipoprotein; MS, metabolic syndrome.

ments for confounding factors [47], the progression of IMT was also slightly greater in metabolic syndrome patients but significance was lost when adjusted for covariates [40].

Management of hypertension with the metabolic syndrome

In the metabolic syndrome, the objective of treatment is both to reduce the high risk of a cardiovascular or a renal event and to prevent the much greater chance that metabolic syndrome patients have to develop type 2 diabetes or hypertension. It is also to delay or prevent progression (as well as to favor regression) of the frequently present types of organ damage carrying an adverse prognostic significance.

Targeting metabolic syndrome mechanisms

Lifestyle measures

The underlying factors promoting development of the metabolic syndrome are overweight and obesity, physical inactivity, and an atherogenic diet. Most individuals who develop the metabolic syndrome first acquire abdominal obesity without risk factors but, with time, multiple risk factors tend to appear, initially with only borderline elevations but then with progressive worsening. Thus, a reduction in body weight by a proper low-calorie diet and an increase in physical activity address the very mechanism of the metabolic syndrome and are hence recommended as just first-line therapy by all current guidelines [48]. A modest caloric reduction (500–1000 cal/day), on the contrary, is usually effective and beneficial for long-term weight loss. A realistic goal is to reduce body weight by 7–10% over a period of 6–12 months. Long-term maintenance of weight loss is then best achieved when regular exercise is part of weight reduction management [49]. Current guidelines recommend a daily minimum of 30 min of moderate-intensity physical activity [50]. Additional increases in physical activity appear to enhance beneficial effects.

Nutritional therapy calls for low intake of saturated fats, trans fatty acids, and cholesterol. Reduced consumption of simple carbohydrates and increased intake of fruits, vegetables, and whole grains is recommended. Extremes in intakes of either carbohydrates or fats should be avoided [50]. Smoking cessation is mandatory. Accumulating evidence suggests that the majority of individuals who develop the metabolic syndrome do not engage in recommended levels of physical activity and do not follow dietary guidelines, for fat consumption in particular [51–53].

Drug treatment

There have been, to date, two types of drugs interfering with the mechanisms of the metabolic syndrome, the insulin-sensitizers and the endogenous cannabinoid type 1 receptor blockers (CB_1 receptor blockers). Although the former increase peripheral glucose disposal by acting in the peroxisome proliferator-activated receptor-gamma (PPAR-γ), the latter reduce abdominal obesity leading to favorable modifications in the status of adipose-tissue typical of this condition.

(a) PPAR-γ agonists: The PPAR-γ regulates genes involved in adipocyte differentiation, fatty acid uptake and storage, and glucose uptake, with a stimulating effect on intravascular lipolysis [54]. Thiazolidinediones, drugs acting as PPAR-γ ligands, may increase lipogenesis in adipose tissue, which decreases serum free fatty acid (FFA) concentrations and increases subcutaneous adipose tissue mass and body weight. Adipose tissue expression and serum levels of adiponectin also increase with administration of thiazolidinediones. This, together with the lowering of serum FFA levels, may contribute to the increased hepatic insulin sensitivity, the reduction of hepatic fat content and the inhibition of hepatic glucose production that are followed by a decrease in plasma glucose and serum insulin levels as well as a reduction of plasma triglyceride and an increase in high-density lipoprotein (HDL)-cholesterol levels. Thiazolidinediones have also been reported to decrease circulating or urinary markers of vascular inflammation that have been shown to be independent predictors of cardiovascular risk, such as plasminogen-activator inhibitor type 1, C-reactive

protein, matrix metalloproteinase 9, and urinary endothelin excretion [54].

Thiazolidinediones have received approval to be used as part of type 2 diabetes treatment but, to date, their use is not recommended for the treatment of insulin resistance in the absence of diabetes, although recent data from the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study have shown that long-term administration of rosiglitazone to subjects with impaired fasting glucose has resulted into a major reduction in the incidence of new-onset diabetes [55].

Systematic reviews of the literature have found no notable benefits of thiazolidinediones with regard to BP, although some evidence points to some BP-lowering effect, at least in type 2 diabetic individuals and in those with refractory hypertension [56]. The increase in body weight resulting from the shift in fat storage from visceral to subcutaneous fat and fluid retention are the main side effects of the drugs, which limits their use. The fluid retention increases the risk to develop congestive heart failure [57]. Concern has also been generated by the report of a meta-analysis in which rosiglitazone administration resulted in an increased incidence of cardiovascular events, although the number of events collected by the data pooling was too small to make the conclusion a definitive one [58]. The increase in cardiovascular risk claimed for rosiglitazone has not been found for pioglitazone according to a recent meta-analysis [59].

(b) Endocannabinoid C_1 receptor blockers: Over the last few years, research has been directed on the role of the endocannabinoid system on appetite, energy expenditure, and metabolism. Cannabinoids and endocannabinoids act via G protein-coupled receptors, the majority of their metabolic-related actions being linked to the endogenous CB_1 receptor [60], represented mostly, though not exclusively, in the central nervous system. The overall effect of inhibition of CB_1 receptors is to decrease appetite and lipogenesis as well as to increase peripheral energy expenditure [61].

A beneficial impact on most of the metabolic syndrome components has been observed with the administration of rimonabant, a CB_1 receptor blocker, in trials [62–65] carried out in overweight and obese subjects with or without dyslipidemia. Body weight and waist circumference were significantly reduced with the administration of the drug that also reduced plasma glucose, plasma triglycerides, and insulin resistance beyond that expected with weight reduction alone. The effects were being complemented by a reduction in HDL–cholesterol. Concerning the BP values, rimonabant 20 mg led to modest but significant SBP and DBP reductions in overweight/obese patients, although the effect appears to be mediated by weight loss [66]. The impact of rimonabant on cardiovascular risk needs to be assessed in prospective studies that also need to collect more data on side effects emerging from the available database, that is, an increase in the incidence of depression and a small but significantly greater risk, in depressed people, of suicide.

Targeting high blood pressure

The threshold for intervention in BP values is based on the recognition that underlying risk factors raise BP to ranges that increase the risk of cardiovascular disease. Consequently, 130/85 mmHg should be the threshold for intervention in the absence of diabetes. Hypertensive patients with the metabolic syndrome should receive hypertensive drugs according to the 2007 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines on hypertension diagnosis and treatment [3]; that is, in addition to recommendations to undergo intense lifestyle modifications, antihypertensive drugs should be given whenever BP is persistently 140 mmHg systolic at least or 90 mmHg diastolic at least. In the presence of diabetes, the threshold for drug intervention should be lower, that is, BP values 130 mmHg systolic at least or 85 mmHg diastolic, whereas the goal BP values should in both instances be less than 130/80 mmHg in line with the goal that is recommended whenever total cardiovascular risk is high [3,67,68]. Similar goals and an even lower threshold for drug intervention ($\geq$130/80 mmHg) should be considered when the metabolic syndrome is present in subjects with a very high cardiovascular risk, such as manifest cardiovascular or advanced renal disease. Which threshold BP for drug intervention should be considered in metabolic syndrome individuals with the metabolic syndrome who have no diabetes, history of cardiovascular, or advanced renal disease is a difficult question because no trial has tested the benefit of antihypertensive drug interventions in this specific population. When microalbuminuria or other types of organ damage of prognostic significance (LVH, carotid atherosclerosis, arterial stiffening) are present, in addition to intense lifestyle changes, administration of antihypertensive drugs should be at least considered with the goal of lowering BP at least to less than 140/90 mmHg and below. Treatment should aim at preventing progression or causing regression of the existing organ damage as well as at reducing the much greater chance an individual with the metabolic syndrome has to develop new-onset diabetes or hypertension. This calls for avoidance of some antihypertensive agents and elective use of some others as outlined in the following section.

Treatments

Ideally, treatment of high BP in the metabolic syndrome should be based on lifestyle changes, diet, and physical exercise, which allows for weight reduction and improves muscular blood flow.

Table 4 Management recommendations for hypertension and the metabolic syndrome

MS component	Threshold	Goal	Recommended	Observations
Elevated BP	130/85 mmHg	<130/80 mmHg[a]	Nonpharmacologic treatment Antihypertensive treatment: First choice: ACEi or ARB Second choice: CCB or β-blockers with vasodilating activity	Thiazide-like diuretics should be avoided in monotherapy or in high-dose β-Blockers should be avoided if not compelling indication exists Combination of thiazide diuretics plus β-Blockers should be avoided

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium-channel blocker; MS, metabolic syndrome. [a]See comment in the text.

Concerning antihypertensive drugs, whether or not a particular antihypertensive agent is superior to others has not been tested in trials including individuals specifically with the metabolic syndrome. A large body of information, however, is available from both long-term antihypertensive trials with major outcomes as well as from a myriad of shorter studies.

After changes in lifestyle are introduced, the drugs to be preferred should be those that may induce reduction of insulin resistance and subsequent changes in the lipid profile and in glucose levels. Therefore, angiotensin-converting enzyme inhibitors (ACEi), angiotensin II-AT1 receptor blockers (ARA II) or even calcium channel blockers are preferable over diuretics and β-blockers in monotherapy, if no compelling indications are present for its use. If a combination of drugs is required, low-dose diuretics can be used. A combination of thiazide diuretics and β-blockers should be avoided (Table 4).

Impact on other metabolic syndrome components

The impact of particular antihypertensive drugs on other components of the metabolic syndrome is an important clinical issue with consequences for the success of the treatment. Changes in metabolic components, mainly in the lipid profile and insulin resistance, during antihypertensive treatment with diuretics and β-blockers have been claimed as the culprit of lower reductions than expected in coronary heart disease morbidity and mortality [69]. On the contrary, reductions in the rates of new-onset diabetes have been observed during treatment with ACEi, angiotensin II-AT1 receptor blockers (ARB) or even calcium channel blockers as compared with diuretics and β-blockers [70,71].

The recently published STAR study (The Study of Trandolapril/Verapamil SR and Insulin Resistance) reduced the risk of new-onset diabetes in obese patients with impaired glucose tolerance, normal kidney function, and hypertension treated with the fixed-dose combination of trandolapril/verapamil as compared to losartan/hydrochlorothiazide-based therapy [72].

For many years, metabolic changes associated with the use of antihypertensive drugs have received attention, looking at both worsening and improvement in the metabolic profile. However, not all the studies report the same conclusions, in part, due to the different dose of the drugs used, particularities of drug mechanisms of action even within the same therapeutic group, duration of treatment and, mainly, because of the different characteristics of the individuals included. Age and hormonal status have been recognized as important modulators of drug impact but, besides these, personal or family histories of metabolic disorders were among the most important factors.

The most recognized metabolic change associated with the antihypertensive drug classes is insulin resistance: it is induced by a combination of different mechanisms including a reduction of the microcirculatory flow in the muscle and a reduction in the rate of intracellular glucose disposal. The former is a consequence of the use of β-blockers, as β-blockade activity goes unopposed by the α-receptors. The latter is not well understood. β-Blocker agents with additional properties can reduce the impact of the pure β-blockade and even exert partially beneficial effects. The simultaneous α-blockade of carvedilol [73] or the increment in the nitric oxide bioavailability of nebivolol [74] have shown a neutral effect on glucose metabolism indexes and a trend towards a favorable lipid profile [75,76].

The potential effect of β-blockers in favoring gaining weight needs to be mentioned. A large review concerning weight changes in studies using β-blockers showed they tend to increase body weight as a consequence of reducing fuel expenditure [77]. The clinical consequences of the gain of weight during β-blocker treatment, however, seem to be negligible.

The reduction of glucose disposal is worse when insulin secretion decreases. This can occur as a direct consequence of the β-blockade, reducing the response of the pancreatic β-cell, and by hypokaliemia induced by thiazide-like diuretics. Reductions in glucose disposal and in the compensatory insulin secretion lead to metabolic abnormalities of the glucose homeostasis and dyslipidemia, as previously described and, in the ELSA study, the incidence of new metabolic syndrome was significantly greater in patients under atenolol than lacidipine [40].

Nevertheless, a beneficial impact of decreasing the risk for the development of diabetes with ACEi-based or ARB-based treatments has been described. Detailed systematic

reviews of the potential beneficial effects have been published recently. In general, treatment with these classes of drugs reduces the rate of new-onset diabetes as compared with the use of diuretic and/or β-blockers [70,71]. Inhibiting the renin–angiotensin system may improve blood flow to muscles, decrease the activity of the sympathetic nervous system, enhance insulin signaling, lower FFA levels, increase plasma adiponectin levels, and improve glucose disposal. Another putative mechanism by which the inhibition of the renin–angiotensin system may improve insulin sensitivity is through effects on PPAR-γ, which is inhibited by angiotensin II [78].

The controversy over whether this effect is a consequence of the risk induced by diuretics or β-blockers and not a real beneficial effect was, in part, resolved by the observation that the reduction in new-onset diabetes was also observed in a trial against placebo [79] and by data furnished by the VALUE study [80,81]. In this study, valsartan-based treatment significantly reduced the rate of new-onset diabetes as compared with amlodipine, a calcium channel blocker. Mechanisms that led to improved glucose metabolism were increment in the microcirculatory flow and in the bioavailability of the Glut4 transporter. The results of the DREAM study [82] challenge the concept of protection against development of new-onset diabetes by using drugs blocking the renin–angiotensin system. The study reports the effects of ramipril on the risk of diabetes in a randomized trial designed with diabetes as a primary outcome in subjects who had impaired plasma glucose levels after an overnight fast or impaired glucose tolerance. Rates of the primary endpoint, mainly diabetes, were not significantly lower in the ramipril group. However, regression to normoglycemia, a secondary outcome, was significantly more frequent in the ramipril group than in the placebo group, although the absolute difference between the groups was small. Several reasons may explain the negative result in the impact of ACEi in to reduce the risk to develop diabetes: there was only 43% of hypertensive patients in the study; these hypertensive patients were under multiple treatments including diuretics and β-blockers; some of the effect can be masked by the treatment with rosiglitazone; and the follow-up of the study was only 3 years, a short period for risk to develop diabetes.

An additional mechanism for some ARBs that has been tested in experimental models is the partial PPAR-γ agonism of telmisartan [83] and even irbesartan [84], with further improvement of insulin resistance. The significance and clinical impact of this additional mechanism, however, need to be tested in appropriately designed studies.

The impact of other antihypertensive drug classes demonstrated the neutral effect of both long-acting calcium channel blockers, as well as other sympathicolytic drugs with central action, such as reserpine, α-methyl-dopa or moxonidine. The pure peripheral α-blocker, doxasozin, improves the lipid profile, reducing insulin resistance and consequently increasing HDL-cholesterol, and reducing triglycerides [69]. A trend to reduce total cholesterol has also been described. The main mechanism implicated in the positive changes of α-blockers seems to be mediated by increasing microcirculation flow. Additional effects of α-blockade on the activity of key enzymes of lipid metabolism are less well known.

A final question is the net effect of the interaction when two different kinds of drugs, with opposite effects, are combined. This is the case of combination treatments with diuretics. Simultaneous administration of a thiazide diuretic with an ACEi or an ARB reduces the hypokaliemia and does not significantly modify the lipid and glucose profile. Whether or not this combination reduces at large the beneficial effects in cardiovascular risk needs to be assessed. A recent publication points out that valsartan alone reduced the levels of high sensitivity C-reactive protein [85]. In contrast, a combination of valsartan plus hydrochlorothiazide, despite a significantly larger BP reduction, was unable to reduce high-sensitivity CPR values. No interaction with statins was demonstrated.

Conclusion

The metabolic syndrome is a highly prevalent condition currently considered to be a cluster of metabolic and cardiovascular risk factors, including BP elevation. A higher risk for progression in metabolic syndrome individuals with high–normal BP has been observed and, when hypertension is established, this seems to confer a higher cardiovascular risk on top of the risk induced by BP elevation. Therefore, assessment of metabolic syndrome components can result in a clinical utility strategy to manage hypertension based on individual risk.

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