Invited review

The metabolic syndrome in hypertension

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Abstract

The metabolic syndrome (MS) is currently considered to be a cluster of metabolic and cardiovascular risk factors including blood pressure elevation. A higher risk to develop hypertension in MS subjects with high-normal blood pressure has been observed and, when hypertension is established, seems to be what confers a higher cardiovascular risk on top of the risk induced by blood pressure elevation. Therefore, assessment of MS components can result in clinical utility strategy to manage hypertension based on individual risk. The main mechanisms for blood pressure elevation include overactivity of the sympathetic and the renin-angiotensin system, abnormal renal sodium handling, and endothelial dysfunction. Treatment aim to reduce the high cardiovascular and renal risk associated with the individual components of MS, and to reduce the risk of developing type-2 diabetes. Diet and regular physical exercise should be strongly recommended. The first choice among the antihypertensive drugs should be those which may induce reduction of insulin resistance and the consequent changes in lipid profile and glucose levels.

Key words: hypertension, metabolic syndrome, obesity, insulin resistance.

Introduction

Arterial hypertension is often part of a constellation of anthropometric and metabolic abnormalities that include abdominal (or visceral) obesity, a characteristic dyslipidaemia (low high-density lipoprotein cholesterol and high triglycerides), glucose intolerance and insulin resistance (IR) and hyperuricaemia. 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 (MS), which has also received different names. Although several definitions of the MS have been formulated the most useful for clinicians are those based on easily collected clinical criteria.

The ATP III [1] and the American Heart Association/National Heart Blood and Lung Institute) (AHA/NHBLI) definition [2] of the MS are based on values for abdominal (central) obesity, dyslipidaemia, and plasma glucose (Table I). For the diagnosis of the MS to be established, the presence of three or more of the listed risk factors is needed. In contrast, in the International Diabetes Federation (IDF) definition [3] central obesity and insulin resistance are regarded as the most important causative factors. Then, central (abdominal) obesity is considered as a prerequisite component for the diagnosis of MS and waist circumference is recommended for its identification, given that the measurement is simple and that its value is independently associated with each MS component,

Table I. Criteria for diagnosing the metabolic syndrome according the Adult Treatment Panel (ATP III), the International Diabetes Federation (IDF) and the American Heart Association (AHA)

Principal criteria	Abdominal obesity	Glucose [mg/dl]	HDL [mg/dl]	Triglyc. [mg/dl]	BP [mm Hg]
ATP III [1]	M ≥102 cm W ≥88 cm	≥110* (6.1 mmol/l)	M ≤40 (1.03 mmol/l) W ≤50 (1.29 mmol/l)	≥150 mmol/l	(1.7 ≥135/85)*
AHA [2]	M ≥94 cm W ≥80 cm	≥100* (5.6 mmol/l)	M ≤40 (1.03 mmol/l) W ≤50* (1.29 mmol/l)	≥150* (1.7 mmol/l)	≥135/85*
IDF Central obesity [3]	M ≥94 cm W ≥80 cm	≥100* (5.6 mmol/l)	M ≤40 (1.03 mmol/l) W ≤50* (1.29 mmol/l)	≥150* (1.7 mmol/l)	≥135/85*

*Diagnosis of metabolic syndrome is based on: a) principal criteria plus at least two others; b) in those without principal criteria, at least three M – men, W – women, *or in treatment for*

including IR [4, 5]. The proposed cut-off points for waist circumference, given in Table I, are recommended to be gender- and ethnic- (not country) specific and more sophisticated measurements of lipid alterations termed atherogenic dyslipidaemia are also considered. Atherogenic dyslipidaemia describes the combination of elevated triglycerides and low HDL cholesterol together with elevated apolipoprotein B (ApoB), small dense LDL, and small HDL particles, all of which are independently atherogenic [6], which is commonly observed in patients with both type-2 diabetes and the MS.

Some authors and scientific societies, however, have claimed that the MS is not a single pathophysiological entity [7, 8]. Although the causes and mechanisms of the MS may indeed be diversified, there is evidence that the overall CV risk accompanying this condition may be greater than the sum of its identifiable components [9]. Simple and easy identification of the MS favours its use in clinical practice, which resists the use of more complex charts for total CV risk quantification, ultimately helping implementation of CV prevention.

The MS 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 CV and renal events even in the absence of overt diabetes. In the present paper, the prevalence, mechanisms, prognostic significance and treatment of the MS in hypertensive patients are reviewed.

Prevalence

Although the prevalence is high in the general population, wide variation in the prevalence of the MS between populations has been reported, with a somewhat higher prevalence in males than females [10]. Metabolic syndrome increases with age and in subjects with diabetes the MS is much more common than in the general population, with rates that approximate 80-90% [11, 12].

Among essential hypertensives, MS prevalence is also higher than in the general population [13-17]. Significant findings are that also among hypertensives MS prevalence is closely related to age (the older the subjects, the higher the prevalence) and that this condition is more commonly found in subjects from referral clinics as compared to those coming from primary care. Among 16,000 hypertensive subjects over 55 years old, recruited in primary health care centres of Spain, the prevalence was 32.6% [18], with obesity being the second, after hypertension, most frequent component of the syndrome, 43.2% in females and 33.5% in males.

A higher prevalence of the MS has been reported among uncontrolled hypertensives as compared to subjects with blood pressure under control by treatment [13]. This may reflect the reduced ability of treatment to lower in subjects with a cluster of cardiovascular risk factors in whom subclinical end-organ damage may concomitantly be more common.

Mechanisms of the metabolic syndrome

The metabolic syndrome is the result of interactions among a large number of interconnected mechanisms, which eventually lead to both an increase in cardiovascular and renal risk, and the development of diabetes. 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. Each organ or cell type is typically both a target and an effector. In general, this situation has been defined by Unger as "a failure of the system of intracellular lipid homeostasis which prevents lipotoxicity in organs of overnourished individuals" [19].

Mechanisms involved in MS are obesity, IR and a constellation of independent factors, which include molecules of hepatic, vascular, and immunological origin with pro-inflammatory properties. Although IR is associated with obesity and central adipose tissue, not all obese subjects have IR. 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 points, IR and obesity/pro-inflammatory molecules, are interactions of demographics, lifestyle, genetic factors, and environmental fetal programming. Superimposed upon these are infections and/or chronic exposure to certain drugs, which can also make their contribution. All interact to create the final individual phenotype [2, 20-22].

Abnormalities in the **structure and function of adipose tissue,** mainly in visceral fat, have been identified as early events which preclude the development of the other features of the MS, including impaired glucose homeostasis [23]. The first structural event which follows from fat tissue increase is the infiltration of adipose tissue by bone marrow-derived macrophages in response to as-yet-unknown signals [24, 25]. This is both a paracrine regulator of adipocyte function influencing free fatty acid (FFA) liberation and hormone secretion of leptin and adiponectin, as well as a source of the inflammatory mediators interleukin 6 (IL-6) and tissue-necrosis factor α (TNF-α) released by adipose tissue. Besides the structural changes, various functional abnormalities of adipose tissue-derived products have been described. These include an increase in FFA, leptin and cytokine release, and a reduction in adiponectin secretion.

A second key issue in the development of MS is **insulin resistance**. It is established in the skeletal muscle and the liver as a result of the inhibition of insulin-stimulated glucose transport activity mainly by accumulation of acyl CoAs and diacylglycerol in the cytoplasm [26]. This increases serine kinase activity, which leads to the suppression of insulin signalling by reducing IRS-2 and Glut-4 transport [27]. Several mechanisms contribute to the intracellular lipid accumulation in muscle and liver and, consequently, to IR. The key mechanisms, however, seem to be an increased release of free fatty acid and cytokines from adipose tissue [28-30] and/or a decrease in mitochondrial oxidation capacity [31, 32]. Insulin resistance and the consequent hyperinsulinaemia have always been considered key elements in the development of MS, although IR is strongly associated with atherogenic dyslipidaemia and inflammation, whereas its mechanistic link with other MS components, such as hypertension and a prothrombotic state [33], is less well established.

Hypertension in the metabolic syndrome

Hypertension is frequent in MS, and more so is blood pressure abnormality, values in the high normal range, which represents one of the 5 components that lead to the identification of this condition. In the PAMELA population study, for example, blood pressure in the high normal or frankly hypertension range was found in more than 80% of the individuals with MS, followed in decreasing order of prevalence by visceral obesity, lipid abnormalities and impaired fasting glucose. The high prevalence of BP abnormalities in the MS explains the very frequent occurrence of subclinical organ damage of the type that is frequently associated with and dependant on blood pressure elevation, such as left ventricular hypertrophy, arterial stiffening and increased urinary protein excretion [34]. Some of these types of organ damage, however, show increased prevalence also in individuals who have MS without blood pressure elevation to the hypertensive level, suggesting that other components of this condition play a role independently of BP.

The two main components of the MS, obesity and IR, may play an important role in the increment of blood pressure and the development of hypertension, although the precise mechanisms that are involved remain partially unresolved (mechanism Redon). Factors commonly associated with and partly dependant on obesity and IR, such as overactivity of the sympathetic [35] and stimulation of the renin-angiotensin systems [36], abnormal renal sodium handling [37], and endothelial dysfunction [38, 39], need to be considered (Figure 1).

Overactivity of the **sympathetic nervous system** is a common feature of obesity in humans, and may play an important role in the frequent association of this condition with hypertension. Compared to lean people, obese individuals have increased levels of plasma norepinephrine, faster urine turnover of norepinephrine in peripheral tissues and increased muscle sympathetic activity, as measured directly by microneurographic methods [40]. Long-term sympathetic activation in MS may raise blood pressure through multiple mechanisms, including an increase in renal tubular sodium

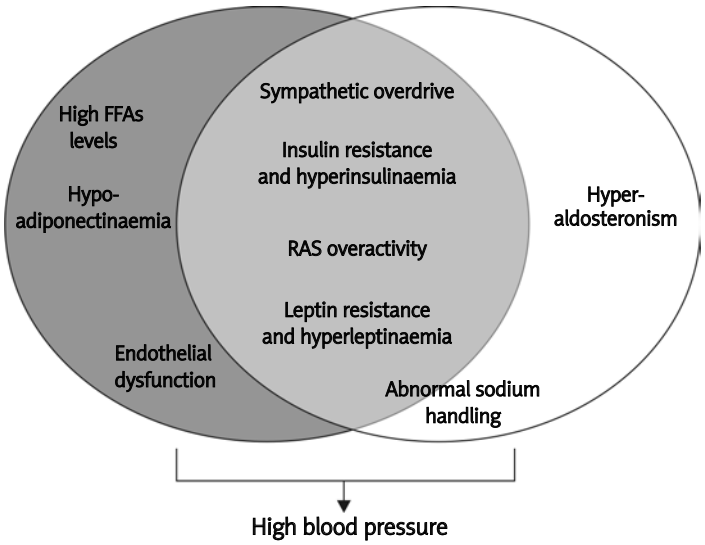

Figure 1. Interaction among the mechanisms leading to high blood pressure

reabsorption [41], systemic vasoconstriction and/or remodelling of the arterioles leading to an increase in their wall-to-lumen ratio and a consequent structural increment in vascular resistance [42]. A wide review of the role of the sympathetic nervous system in the MS has recently been published [43].

The activity of the **renin-angiotensin system** (**RAS**) is increased in most obese individuals despite the fact that obesity is accompanied by sodium retention and increased extracellular fluid volume, which should inactivate renin release from the kidney and angiotensin II formation. The cause of RAS activation may be enhanced renin production due to diminished sodium delivery to the macula densa because of its greater reabsorption in the loop of Henle. Stimulation of renin release by the increased sympathetic nerve activity to the kidneys may also be involved, however [37, 44]. Finally, an increase of angiotensinogen formation in adipose tissue may contribute to the RAS activation. Angiotensin II enhances tubular sodium reabsorption [45], increases peripheral arterial resistance [44] and stimulates the sympathetic nervous system.

Recently, the role of aldosterone in obesity-associated hypertension has been emphasized. Plasma aldosterone levels are elevated in hypertensives with visceral obesity [46]. Although the mechanisms implicated in the overproduction of aldosterone are not well delineated, attention has been directed to the production of potent mineralocorticoid-releasing factors in fat tissue [47] as well as to the ability of oxidized derivatives of linoleic acid to induce aldosterone synthesis [48]. Aldosterone may raise blood pressure in obesity also through an action on mineralocorticoid receptors located not only in the kidney but also in the vasculature and the brain.

When associated with weight gain hypertension is accompanied by increased sodium reabsorption and impaired **renal-pressure natriuresis.** This can result from the increased sympathetic activity typical of both obesity and hypertension, as well as by the concomitant RAS activation, hyperaldosteronism, and altered renal haemodynamic and intrarenal physical forces [49]. Glomerulosclerosis develops as the result of long-term hyperfiltration, and contributes to the sodium dependency of the elevated blood pressure values in a more advanced stage [50].

Various components of the MS have an adverse impact on the **endothelium**, leading initially to oxidative stress, reduced citric oxide bioavailability and a dysfunctional state and, later, to vascular damage [51]. Endothelial dysfunction is reflected by the presence of impaired endothelium-dependent vasodilatation as well as by the activation of inflammatory, proliferative, and coagulation markers that are responsible for the pro-inflammatory and pro-coagulant states frequently seen in the MS.

What causes the endothelial dysfunction in the MS is still not entirely clear, although there are several factors which can contribute to it. Insulin-resistant states are characterized by blunted insulin-mediated vasodilatation because of impairment of the phosphoinositol pathway (PI-3) which may lead to a decrease in eNOS activity, and consequently lower nitric oxide production. The adverse consequences of these phenomena may be enhanced by the fact that since the MAP-kinase pathway is unaffected by insulin, there may be unimpaired synthesis of endothelin 1 (ET-1), which

favours vasoconstriction [52], vascular smooth muscle cell growth and cell migration from the vessel medial to the internal layer. This may promote an increase in vascular stiffness and thickness, favouring the cascade of events that are responsible for formation and progression of the atherosclerotic plaque. Taken together, these phenomena may explain at last in part the increased BP and cardiovascular risk associated with hyperinsulinaemia [51, 53].

A close association between hypoadiponectinaemia and endothelial dysfunction has also been demonstrated. Low plasma adiponectin levels have been shown to be associated with impaired endothelium-dependent vasodilatation [54], generating the hypothesis that hypoadiponectinaemia contributes to the development of obesity-related hypertension via a direct effect on the vasculature. Whether or not adiponectin supplementation may represent a potentially useful therapeutic modality in MS individuals with or without hypertension requires further studies [55].

Finally, plasma FFA elevation also impaired endothelial-dependent vasodilatation. FFA reduces the circulating levels of most amino acids, including L-arginine (i.e. the substrate for NO production) [56], and inhibition of nitric oxide production by these compounds has been described. Acute short-lasting increases in FFA plasma level which follow a high lipid content meal induced transitory endothelial-dependent vasodilatation [57].

Metabolic syndrome and hypertension-induced organ damage

Recent studies have reported an increased prevalence of left ventricular hypertrophy (LVH), diastolic dysfunction, carotid atherosclerosis, impaired aortic distensibility, hypertensive retinopathy and microalbuminuria in hypertensive patients with MS when compared to those without it (position statement Redon). Because most of these kinds of organ damage are recognized as significant independent predictors of adverse cardiovascular and renal outcomes, this may partially explain the association of the MS with a higher risk of CV event and renal disease.

Several studies have demonstrated that the MS is associated with a high prevalence of LVH in hypertensives and that this is the case throughout a wide age spectrum. Moreover, the number of MS components has been directly related to the risk of having EKG [58] and echocardiographic LVH [16, 17, 59], although this has not been confirmed in other studies [60, 61]. The effect of the MS on LV structure has been reported to be more pronounced in women than in men, and shown to be partly independent of the effect of haemodynamic and non-haemodynamic determinants of LV mass [62] including blood pressure values over 24 h [34]. Atrial enlargement, a prognostic factor for the development of atrial fibrillation and stroke, has also been associated with overweight, high fasting glucose and the MS, independently of LV mass and geometry [60, 62].

An increase in the prevalence of abnormal urinary albumin excretion has been observed among hypertensives with MS, as compared to those without MS [16, 17, 62, 63], and indeed microalbuminuria has been considered a diagnostic element for MS in early definitions of this condition. The prevalence of microalbuminuria has been shown to increase with the number of MS components, a finding seen also in non-diabetic subjects [16].

The relationship between MS and glomerular filtration rate (GFR) has been analyzed in several population studies, although only a few in hypertensives. In a cross-sectional survey of hypertensives seen in primary care, the MS was associated with lower GFR, estimated by the MDRD formula. Furthermore, the number of MS components was linearly related to the prevalence of GFR <60 ml/min/1.73m^2 [18].

Pulse wave velocity is greater in hypertensives with MS and has also been associated with a faster progression of aortic stiffness with age, independently of major individual CV risk factors [64], suggesting that it may promote premature vascular senescence. Finally, an association between MS and carotid intima-media thickness has been observed in several studies [16, 64 , 65], although to a weaker degree than that observed for markers of organ damage such as LVH and microalbuminuria. In a large survey of Ja-panese subjects [64], it was found that the prevalence of carotid atherosclerosis increased progressively with the number of MS components in hypertensives but not in normotensives.

Prognostic value of the metabolic syndrome in hypertension

A limited number of studies have examined the prognostic importance of the MS and of its individual components in hypertension.

In the Copenhagen Male Study [66], 2,906 male participants were divided into three groups according to their fasting plasma triglyceride and HDL cholesterol levels, two lipid parameters highly related to insulin resistance and hyperinsulinaemia. The CV risk was not increased in patients with hypertension in the absence of the above defined dyslipidaemia. However, the group with high blood pressure and dyslipidaemia was the one displaying the highest risk.

The prognostic significance of MS in hypertension was also analyzed in the PIUMA cohort, which consisted of 1,742 hypertensive patients without CV disease at entry. Over a 10.5-year follow-up, MS patients, as defined by the ATP III criteria, had a CV event rate that was almost double that of the patients without MS. In the MS patients the CV risk remained greater after adjusting for age, gender, total plasma cholesterol serum, creatinine, smoking, LVH and 24-h systolic BP. The presence of MS was an independent predictor of both cardiac and cerebrovascular events and the risk remained higher after removal of diabetic subjects [67].

In a Turkish study, 2,225 men and women, free of CV disease at baseline and with a blood pressure in the high-normal or hypertension range, were followed up for a mean of 4.1 years. Subjects defined as dyslipidaemic hypertensives, based on the blood pressure, plasma triglycerides, and HDL cholesterol criteria for MS identification used by the National Cholesterol Education Program guidelines, had a higher CV risk as compared to hypertensives who did not have dyslipidaemia after adjustment for sex, age, LDL cholesterol, and smoking status. The dyslipidaemic phenotype was associated with half of the attributable CV risk of the MS [68].

In the Hoorn study [69], 615 men and 749 women aged 50 to 75 years and without diabetes or a history of CV disease at baseline were followed over a 10-year follow-up period. With a prevalence of the MS at baseline ranging from 17 to 32%, MS was associated with a higher CV risk and the risk increased with the number of MS components. When the various MS definitions were compared the ATPIII definition was associated with about a 2-fold increase in the age-adjusted risk of fatal CV disease in men and non-fatal CV disease in women. For the WHO, EGIR, and ACE definitions of the MS the hazard ratios per CV events were slightly lower.

The PAMELA study has provided further data on the association of the MS with cardiac organ damage and increased cardiovascular risk [34]. The MS, as diagnosed using the 2003 ATP III criteria, was identified in 16.2% of the 2,051 subjects representative of an urban population from northern Italy, with the prevalence increasing to about 25% in middle-aged and elderly subjects. The most and least frequent MS components were high normal blood pressure and impaired fasting glucose, respectively. Echocardiographically-documented LV hypertrophy was seen more frequently in subjects with than in those without MS (10.6 vs. 20.6%), the difference occurring in males and females, at all ages, and after exclusion from either group of individuals with hypertension (blood pressure ≥140 mm Hg systolic or 90 mm Hg diastolic or use of antihypertensive drugs), as well as after adjustment of data for 24 h mean systolic blood pressure values. Over 148 months of follow-up, the risk of CV and all-cause death was significantly greater in MS individuals, the difference vs. those without this condition remaining significant (about 70 and 40%, respec-tively) after adjustment for differences in age, gender, and other cardiovascular risk factors [34].

Management of the metabolic syndrome

In the MS 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 MS patients have to develop type-2 diabetes or hypertension. It is also to delay or prevent progression (as well as to favour regression) of the frequently present organ damage carrying adverse prognostic significance. Obviously, the best treatment consists in opposing the underlying mechanisms of the MS. This means adopting lifestyle interventions that effectively reduce visceral obesity, a goal which is, however, often difficult to achieve and maintain in the long term. It may also mean making use of drugs that oppose the development of insulin resistance or the hyperactivity that may help body weight gain, although their actual involvement in the MS is still under study. The potential role of insulin sensitizers and endocannabinoid C1-receptor blockers has recently retreated for various reasons [70]. Then it is necessary to treat the individual components of the syndrome in order to achieve a reduction of their contribution to the overall risk level.

Hypertensive patients with MS should receive hypertensive drugs according to the 2007 ESH/ESC guidelines on hypertension diagnosis and treatment [71]. That is because in addition to receiving recommendations to undergo intense lifestyle modifications they should be given antihypertensive drugs whenever blood pressure is persistently ≥140 mm Hg systolic or 90 mm Hg diastolic. In the presence of diabetes the threshold for drug intervention should be lower, i.e. blood pressure values ≥130 mm Hg systolic or 85 mm Hg diastolic, whereas the target blood pressure values should in both instances be <130/80 mm Hg in line with the goal that is recommended whenever total cardiovascular risk is high. Similar goals and an even lower threshold for drug intervention (≥130/80 mm Hg) should be considered when the MS is present in subjects with a very high CV risk, such as in the presence of a history of CV or advanced renal disease.

Which threshold blood pressure for drug intervention should be considered in MS individuals with the metabolic syndrome who have no diabetes

or history of CV or advanced renal disease is a difficult question because no trials have tested the benefit of antihypertensive drug interventions in this specific population stratum. Given their high CV risk, however, it seems logical to suggest that, in addition to intense lifestyle changes, administration of antihypertensive drugs should be at least considered also under this circumstance, with again the goal of lowering blood pressure to <130/80 mm Hg. This should be particularly the case when microalbuminuria or other organ damage of prognostic significance (LVH, carotid atherosclerosis, arterial stiffening) are present. Treatment should aim at preventing progression or causing regression of the existing organ damage as well as reducing the much greater chance an individual with the MS has to develop new onset diabetes or hypertension. This calls for avoidance of some antihypertensive agents and elective use of some others.

Ideally, treatment of high BP in the MS should be based on lifestyle changes, diet and physical exercise, which allows for weight reduction and improves muscular blood flow. Concerning antihypertensive drugs, whether or not a particular antihypertensive agent is superior to others has not been tested in trials including subjects specifically with the MS. 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 used should be those which may induce reduction of insulin resistance and consequent changes in the lipid profile and in glucose levels. Therefore, angiotensin-converting enzyme inhibitors (ACEi), angiotensin II-AT1 receptor blockers (ARAII) or even calcium channel blockers are preferable over diuretics and β-blockers in monotherapy, if no compelling indications are present for their use. If a combination of drugs is required, low-range doses of diuretics can be used. A combination of thiazidic diuretics and β-blockers should be avoided (Table II).

Conclusions

The metabolic syndrome is a highly prevalent condition currently considered to be a cluster of metabolic and cardiovascular risk factors including blood pressure elevation. A higher risk to progress in MS subjects with high-normal blood pressure has been observed and, when hypertension is established, seems to be what confers a higher cardiovascular risk on top of the risk induced by blood pressure elevation. Therefore, assessment of MS components can result in a clinical utility strategy to manage hypertension based on individual risk. Development of hypertension is commonly associated with both obesity and IR. The main mechanisms include overactivity of the sympathetic and the reninangiotensin system, abnormal renal sodium handling, and endothelial dysfunction. The objectives of MS treatment in the hypertensive patient are both to reduce the high cardiovascular and renal risk associated with the individual components of MS, and to reduce the risk of developing type-2 diabetes. Diet and regular physical exercise should be strongly recommended. The first choice among antihypertensive drugs should be those which may induce reduction of insulin resistance and the consequent changes in lipid profile and glucose levels. Beside close blood pressure control, LDL cholesterol and glucose levels should be targeted to be reduced as much as possible. Drugs improving insulin resistance may contribute to controlling components of the MS, although further knowledge on cardiovascular and renal morbidity and mortality needs to be obtained from current ongoing studies.

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Table II. Management recommendations for hypertension and metabolic syndrome (position statement of the ESH) [70]

MS component	Threshold	Target	Recommended	Observations
High blood pressure	130/85 mm Hg	<130/80 mm Hg	Non-pharmacological treatment	Thiazide-like diuretics should be avoided in monotherapy or in high dose
			Antihypertensive treatment:	
			First choice: ACEi or ARB	β-blockers should be avoided if no compelling indication exists
			Second choice: CCB or β-blockers with vasodilatory activity	Combination of thiazide diuretics plus β-blockers should be avoided

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