Metabolic Syndrome in Hypertension.
Treatment Challenges and Goals

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Abstract
Changes in lifestyle in the developed world are promoting the epidemic growth of overweight and obesity, leading to several metabolic abnormalities (lipids, glucose and blood pressure), and increasing the future risk of type 2 diabetes, cardiovascular events and death. Metabolic syndrome represents the combination of abdominal obesity, insulin resistance, atherogenic dyslipidemia, and prothrombotic and proinflammatory states. Although some controversies in the pathogenesis and clinical importance of metabolic syndrome still remain, the development of useful clinical tools to identify these patients more easily has derived to an increased recognition in the adult population. Management of patients with metabolic syndrome is a clinical challenge and requires a multifactorial, multidisciplinary approach. Changes in lifestyle are obviously the first therapeutic step and include both dietary modifications and increased daily exercise. Several questions remain to be elucidated with respect to pharmacological treatment. The blood pressure levels required to initiate antihypertensive treatment, the blood pressure goal to be achieved and the possibility of including a renin-angiotensin system blocker as a part of the pharmacological treatment are still under discussion. Moreover, there is lack or poor evidence on the need for specific drugs to reduce triglycerides, to increase HDL-cholesterol, to improve insulin sensitivity or to decrease abdominal obesity. Independently, it is generally accepted that earlier and more aggressive therapy in subjects with metabolic syndrome will result in a decrease of the future cardiovascular morbidity and mortality worldwide.

Keywords: Cardiometabolic risk, metabolic syndrome, hypertension, antihypertensive agents, type 2 diabetes.

The concepts of metabolic syndrome and cardiometabolic risk
Cardiometabolic risk represents a situation where the possibilities of developing atherosclerotic cardiovascular disease and diabetes mellitus are significantly enhanced as a consequence of the presence of insulin resistance and atherogenic dyslipidemia, this latter characterized by the presence of low HDL-cholesterol and high triglyceride levels [1,2]. The clinical diagnosis of this situation is made through the finding of an enhanced waist circumference (above 102 cm in males and 88 cm in females) accompanied by the above quoted alterations in lipid profile (HDL-cholesterol below 40 mg/dl in males and 50 mg/dl in females and serum triglycerides above 150 mg/dl).

Cardiometabolic risk is particularly prevalent in patients diagnosed as having metabolic syndrome (MS), which in turn requires for a correct diagnosis besides an increased waist circumference, a low HDL-cholesterol and elevated triglycerides, the potential presence of blood pressure (BP) values above 130/85 mmHg and a fasting serum glucose above 100 mg/dl [3,4]. The International Diabetes Federation has also defined the MS in Europids by the presence of a waist circumference above 94 cm in males and 80 cm in females accompanied by the finding of two out of the other four criteria that remain unchanged as compared to the ATP-III definition [5]. Recently, a consensus document [6] signed by the International Diabetes Federation, the National Heart, Lung, and Blood Institute, the American Heart Association, the World Heart Federation, the International Atherosclerosis Society and the International Association for the Study of Obesity has been released, harmonizing these different criteria definition of metabolic syndrome. The document does not consider obesity as a prerequisite for the definition (as stated in the IDF criteria) and maintain the possibility of all 3-factor combinations among the 5 possible alterations. This is in agreement with the previous reports from NCEP/ATP III [3] and NHLBI/AHA [4], with the exception of the definition of elevated waist circumference, with different thresholds depending on ethnicities. For people of Caucasian origin, including Europids, the level of waist circumference above 94 cm in men and 80 cm in women must be considered as increased risk, although the threshold of the waist circumference above 102 cm in men and 88 cm in women, defines the level at which the risk is substantially higher and probably must be considered as the definition criteria of abdominal obesity.

¿How frequent and relevant is the metabolic syndrome in the hypertensive population?
The prevalence of MS in the hypertensive population is very high. In a study with more than 19000 hypertensive patients attended in primary care centres in Spain, MS was present in more than 40% of subjects, by using the original ATP III definition [3] and increased until 60% when the IDF criteria [5] was applied [7].

Metabolic syndrome and consequently increased cardiometabolic risk are then very prevalent in the hypertensive population and need to be incorporated to a correct stratification of risk that has to be done in every hypertensive patient. In fact, the Guidelines of the European Society of Hypertension- European Society of Cardiology [8,9] consider the concomitant finding of arterial hypertension and MS syndrome as a situation of high-added cardiovascular risk. The reason to do this is based on two facts. Firstly, metabolic syndrome and the accompanying cardiometabolic risk result in a significant increment in
cardiovascular morbidity and mortality in several population-based studies, as previously reviewed[10], as well as in hypertensive patients[11]. Secondly, the presence of metabolic syndrome is accompanied by a 3-6 times increase in risk of developing type 2 diabetes[12].

On the other hand the presence of MS is accompanied by a significant enhancement in the risk of developing chronic kidney disease (albuminuria and/or a diminished estimated glomerular filtration rate). The higher the number of components used for the definition of metabolic syndrome the higher will be the prevalence of either microalbuminuria and/or an estimated GFR value < 60 ml/min/1.73 m²[13].

¿How relevant is the development of diabetes mellitus in a hypertensive population?
The development of new onset diabetes and its relevance in hypertensives has been widely considered [14,15]. The type of antihypertensive therapy used, alone or in combinations, is relevant to accelerate the appearance of diabetes. A network meta-analysis[16] has shown that the best protection is obtained when angiotensin receptor blockers and converting enzyme inhibitors are used, while diuretics and beta blockers are occupying the last position in particular when used in combination.

Albeit some authors have denied that the development of new onset diabetes contributes to worsen the short-term prognosis of hypertensive patients according to the data of studies like SHEP[17] and ALLHAT[18], it seems clear that becoming a diabetic must be relevant for the long-term patient’s prognosis. In fact, it has been shown that with 2 and a half years of follow-up above that in ALLHAT the risk of new diabetics was equal to that of patients entering the study as declared diabetics[19].

¿How should a patient with hypertension and metabolic syndrome be treated?
The aim of intervention in patients with MS and high cardiometabolic risk is to achieve an optimal reduction of such risk. Lifestyle modifications counteract the effect of the underlying risk factors (obesity, physical inactivity and atherogenic diet). Moreover, hypertensives also require a tight BP control, a choice of antihypertensive treatment not producing other metabolic disturbances, and quite often parallel drug treatment for associated metabolic risk factors (dyslipidemia, insulin resistance and prothrombotic and proinflammatory states).

Lifestyle interventions
They are obviously the first step in achieving the goal of cardiometabolic risk reduction. The key lifestyle interventions are the promotion of exercise and energy expenditure and the reduction of overweight by caloric restriction[20]. The minimal requirements for long-term effectiveness include caloric restriction in the range of 500-1000 Kcal with a 7%-10% weight loss in 12 months and regular aerobic exercise of 30-45 minutes daily. Whereas extreme caloric-restricted or element dissociated diets have no long-term advantages, more intensive exercise programs have additional cardiovascular benefits and help to maintain weight loss. Lifestyle interventions have clearly beneficial effects on BP and the lipid profile and reduce the incidence of new-onset diabetes[19]. Moreover, recent data suggest a long-term effect on the reduction in cardiovascular morbidity[21].

Other lifestyle changes also have a beneficial effect on specific CV risk factors and must be encouraged in specific patients. Lowering salt intake and alcohol consumption have moderate BP lowering effects, which are enhanced in conjunction with weight loss and increased exercise[8]. In addition, a diet rich in fruits, vegetables and low-fat dairy products (DASH diet) substantially lowers BP in comparison to the standard American diet[22]. Also the Mediterranean diet, which is equally rich in fruits, vegetables, fish and olive oil, has a favourable impact on atherogenic dyslipidemia in MS patients[24].

Maintenance of lifestyle changes requires counselling and may prove difficult in the long term. For this reason, pharmacological treatment of BP, dyslipidemia, insulin resistance and obesity will be required for most patients to reduce cardiometabolic risk[26].

Antihypertensive therapy
As mentioned above, the European Society of Hypertension / European Society of Cardiology Guidelines[8,9] emphasize the importance of metabolic syndrome as an indicator of high added cardiovascular risk in hypertensives, thus indicating early antihypertensive treatment if lifestyle measures are not enough to reach BP targets.

No comparative studies of the different antihypertensive drug classes in hypertensives with metabolic syndrome are available. However, considering the increased risk of developing new-onset diabetes in these subjects, as one of the components of cardiometabolic risk, the choice of antihypertensive treatment must take this additional risk into account. Some international guidelines recommend diuretics as the first-step therapy for hypertensive patients without a compelling indication for other antihypertensive drug classes. However, it has been clearly established that diuretics increase the risk (23%) of new-onset diabetes compared to placebo[16]. Conversely, calcium channel blockers and, especially, renin-angiotensin system blockers (angiotensin receptor blockers and angiotensin-converting-enzyme inhibitors) decrease this risk (33% with ACE inhibitors and 43% with angiotensin receptor blockers). These differences are probably even more pronounced in the specific subset of patients with MS. Thus, it seems reasonable that the first consideration in antihypertensive treatment in hypertensives with MS and high cardiometabolic risk should focus on the inhibition of the renin-angiotensin system with either ACE inhibition or angiotensin blockade.

Additional evidence can be derived from comparative studies of antihypertensive drugs that have included an important proportion of diabetic subjects, most of them also suffering from MS. In this regard, the Appropriate Blood Pressure Control in Diabetics (ABCD)[28] compared in the subset of hypertensive diabetics, antihypertensive treatment based on the ACE inhibitor enalapril or the calcium channel blocker nisoldipine. The study was prematurely halted due to differences in the number of myocardial infarction that favoured enalapril in comparison to nisoldipine.

Hypertensive patients with metabolic syndrome and especially those with type 2 diabetes are often resistant to the effects of
antihypertensive drugs and may require drug combinations to achieve blood pressure control. Although some studies have demonstrated the benefits of using diuretics in combination with ACE inhibitors [27] or ARBs [28] in diabetics, two comparative studies suggest that combining a renin-angiotensin blocker with a calcium channel blocker could be a better option. The Anglo Scandinavian Cardiac Outcome Trial (ASCOT)[29] compared antihypertensive treatment based on the calcium channel blocker amlodipine with the addition in most patients of the ACE inhibitor perindopril against the beta blocker atenolol with the addition of a thiazide diuretic also in the vast majority of patients. The study was also prematurely interrupted due to a consistent benefit of the former therapeutic option. More than 5000 diabetic patients were included in ASCOT and a particular analysis of this cohort revealed that the benefits of the combination of amlodipine and perindopril were maintained in diabetics[30]. Another study, the ACCOMPLISH trial [31] also compared 2 combinations of antihypertensive agents in high-risk hypertensives. Patients were treated with either the combination of the ACE inhibitor benazepril and the calcium channel blocker amlodipine or benazepril combined with hydrochlorothiazide. The proportion of diabetics in this study reached 60%. Main results revealed a 20% reduction in the primary endpoint in patients treated with benazepril amlodipine combination. Subgroup analyses did not find heterogeneity of the results in subjects with or without diabetes.

No evidence supports a preference for ACE inhibitors or ARB’s in the treatment of MS patients. The ONTARGET [32] trial compared telmisartan with ramipril in patients at risk for cardiovascular events (one third with diabetes) and found no differences in rates of cardiovascular events between groups.

It has been hypothesized that the particularity of some angiotensin receptor blockers acting as modulators of the nuclear receptor PPAR-gamma[33] could be important for additional metabolic benefits of these drugs. Comparative studies of telmisartan, the ARB with a more potent ability to stimulate the PPAR-gamma receptor, against losartan[34], irbesartan[35] or eprosartan[36] resulted in better metabolic outcomes, as measured by fasting glucose, insulin and lipids. However, in the ONTARGET trial rates of new onset diabetes were not different in ramipril or telmisartan treated patients[32].

Non-hypertensive patients with metabolic syndrome usually have high-normal BP (systolic 130-139 mmHg and/or diastolic 85-89 mmHg). Specific dietary interventions, such as sodium restriction or the adoption of the DASH diet, in addition to caloric restriction and increased exercise, could be helpful. For patients also having diabetes antihypertensive treatment with renin-angiotensin blockers is able to prevent the development of microalbuminuria in normoalbuminuric patients[37] or overt proteinuria in those having microalbuminuria[38]. For the remaining subjects, no evidence is available for antihypertensive treatment, except that hypertension development is prevented[39].

**Other drugs that could add benefit in patients with metabolic syndrome**

*Lipid-lowering therapy*

The ASCOT Trial demonstrated that treatment with 10 mg atorvastatin was effective in reducing cardiovascular events when hypertension was accompanied by 3 or more additional risk factors, including most that are contained in the definition of metabolic syndrome[40]. However, the typical dyslipidemia in hypertensives with MS is characterized by low-HDL cholesterol and increased triglycerides. Two classes of drugs reduce triglycerides and increase HDL-cholesterol. These are nicotinic acid and fibrates. Although limited evidence is available, some post-hoc analyses suggest a beneficial effect of these drugs in patients with metabolic syndrome[41,42].

**Insulin sensitizers**

In addition to lifestyle changes, treatment with metformin[19], acarbose[43] and thiazolidinediones[44] decreases the risk of new-onset diabetes in patients with impaired glucose tolerance. However, the long-term benefits of these drugs and the cost-benefit analysis have not been adequately addressed.

**Antiobesity drugs**

Abdominal obesity is one of the main components of MS and increased cardiometabolic risk. In addition to a restricted caloric diet and increased exercise, several pharmacological approaches have been tested in these patients. Although effective in reducing weight and waist circumference, drugs such as sibutramine or rimonabant withdrew from the market due to unacceptable side effects and only orlistat, an inhibitor of gastrointestinal lipases, especially pancreatic lipase, is available. Orlistat promotes a moderate weight loss and also has a favourable influence on lipids and glycemic control, especially in diabetics, although gastrointestinal tolerance is poor[45]. The need of new pharmacological approaches to abdominal obesity with efficacious, but also safe drugs, is a pharmaceutical urgency.

**Antithrombotic drugs**

A key feature of metabolic syndrome that explains the increased cardiometabolic risk is an enhanced prothrombotic state, especially in the presence of insulin resistance. Postprandial hyperglycemia, increased free fatty acids and elevated triglyceride levels may all have adverse effects on platelets, coagulation and fibrinolysis. Pharmacological interventions targeting these abnormalities have the potential to reduce thrombosis. Antiplatelet drugs such as low-dose aspirin have proven benefit in patients with previous CV disease, but extension to other groups, including diabetics is controversial[46]. Efforts to control BP should be reinforced before the introduction of aspirin.

**Closing remarks**

Although there are several areas of uncertainty with respect to the definition, usefulness and pathogenesis of MS, simple clinical tools exist which identify subjects at a higher risk of developing both type 2 diabetes and cardiovascular disease, and thus having high cardiometabolic risk. The management of these subjects is based principally on lifestyle measures, but various antihypertensive, lipid-lowering, insulin sensitizing, antiobesity and antiplatelet drugs could be helpful in reducing the cardiometabolic risk. This is particularly important in the hypertensive population. The presence of MS identifies individuals with high cardiometabolic risk who require an integrated therapeutic approach, considering an earlier use of
specific antihypertensive drugs that do not increase the risk of type 2 diabetes, as well as other therapies counteracting the associated metabolic alterations present in every single patient.

Population-based strategies are clearly necessary to reduce the impact of underlying risk factors for cardiometabolic risk (obesity, physical inactivity and atherogenic diet). However, there is general agreement that earlier and more aggressive therapy is required to further reduce the risk of new diabetes and cardiovascular disease, although evidence is scarce. Prospective, randomized trials addressing the effect of potentially beneficial treatments on cardiometabolic outcomes should be strongly encouraged.

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