Journal of
HYPERTENSION RESEARCH
www.hypertens.org/jhr

Editorial Foreword
J Hypertens Res (2020) 6(3):59-66

Antihypertensive medication in metabolic syndrome

Victor A. Voicu *

Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Received: July 29, 2020, Accepted: September 2, 2020

Abstract

Antihypertensive agents are – by means of their pharmacodynamics diversity – inevitably targeted at various, complex and interrelated bonds involved in the homeostasis of blood pressure. Realistically speaking, the therapeutic approach of arterial hypertension in the context of metabolic syndrome, whether it is considered a risk factor or a disease, a pathological entity, includes without exception comorbidities, known for being generally present under different practical connotations. This context is a limiting factor for the freedom of choosing among various available antihypertensive drugs. The antihypertensive treatment plan will certainly differ from a patient with essential hypertension and no significant comorbidities to other patients suffering from multiple comorbidities such as chronic limb ischemia, kidney failure, asthma, heart failure, metabolic syndrome, diabetes mellitus, history of cerebrovascular accident, or myocardial infarction, ischemic cardiomyopathy, depressive disorder and so on. What are the pathological issues of metabolic syndrome? What would determine certain restrictions in the antihypertensive treatment options, absolute or relative contraindications, avoidance of pharmacological interactions, and so forth? Restrictions apply to whether direct or indirect consequences regarding pharmacotherapeutic effects, the result of pharmacokinetic processes' biotransformation (metabolism, excretion) of specifically recommended medications. We emphasize the fact that hypertension is part of the metabolic syndrome conceptual definition.

Keywords: Hypertension, metabolic syndrome, pharmacotherapy.

Background

Antihypertensive agents are – by means of their pharmacodynamics diversity – inevitably targeted at various, complex and interrelated bonds involved in the homeostasis of blood pressure [1].

* Correspondence to: Acad. Victor A. VOICU, MD, PhD
Carol Davila University of Medicine and Pharmacy,
8 Calea Floreasca, Bucharest, Romania
Phone: +40215992300

In essence, the mechanisms and sites of action for antihypertensive drugs target both central and peripheral components of the sympathoadrenal system, along with natremia and plasmatic volume, calcium influx restriction – which implies the uncoupling of excitation-contraction in the vascular smooth muscle cells – the renin-angiotensin-aldosterone system control, vasopeptidase inhibitors, redox and inflammation homeostasis, ACE2 and Mas receptors activation axis and others.

Realistically speaking, the therapeutic approach of arterial hypertension in the context of metabolic syndrome, whether it is considered a risk factor or a disease, a pathological entity, includes without

exception comorbidities, known for being generally present under different practical connotations. This context is a limiting factor for the freedom of choosing among various available antihypertensive drugs.

The antihypertensive treatment plan will certainly differ from a patient with essential hypertension and no significant comorbidities to other patients suffering from multiple comorbidities such as chronic limb ischemia, kidney failure, asthma, heart failure, metabolic syndrome, diabetes mellitus, history of cerebrovascular accident, or myocardial infarction, ischemic cardiomyopathy, depressive disorder and so on.

What are the pathological issues of metabolic syndrome? What would determine certain restrictions in the antihypertensive treatment options, absolute or relative contraindications, avoidance of pharmacological interactions and so forth?

Restrictions apply to whether direct or indirect consequences regarding pharmacotherapeutic effects, the result from pharmacokinetic processes' biotransformation (metabolism, excretion) of specifically recommended medications. We emphasize the fact that hypertension is part of the metabolic syndrome conceptual definition [2].

Metabolic syndrome

Formerly known as syndrome X, metabolic syndrome or cardiometabolic syndrome was described by Gerald Reaven, highlighting one main characteristic – insulin resistance [3–5].

Insulin resistance is associated with obesity (central obesity) and a constellation of other heavily relevant independent pathological factors, respectively, a set of hepatic, vascular and immunological molecular factors with proinflammatory properties.

The three categories of factors focus on:

1. Insulin resistance
2. Obesity
3. Proinflammatory factors interfering with lifestyle, genetic and environmental factors [6]

Interaction of previously mentioned factors defines the individual phenotype decisively, altering the regulatory mechanisms involved in blood pressure homeostasis.

P.A. van Zwieten et al. (2006), approaching pharmacological treatment issues of metabolic syndrome, records four characteristics (components) of this syndrome: changes in glucose tolerance and insulin resistance, abdominal (visceral) obesity, atherogenic dyslipidemia and hypertension. The World Health Organization (WHO) includes in that definition albuminuria both as a kidney injury detection marker and an early sensitive predictor for initial stages of cardiovascular disease [7].

The pathophysiology of metabolic syndrome comprises associated factors, partially depending on insulin resistance and obesity, sympathoadrenal hyperactivity, increased activation of the renin-angiotensin-aldosterone system, disruption in the control of renal sodium excretion and endothelial dysfunction [6].

It is accepted that the association between metabolic syndrome and arterial hypertension induces multiple injuries in targeted organs.

Thus, left ventricular hypertrophy is observed; structural alterations of the left ventricle are more noticeable in women rather than in men. Atrial enlargement – predicting factor for atrial fibrillation and ischaemic stroke – is associated with metabolic syndrome regardless of left ventricular mass and geometry [6].

Albuminuria is frequently observed in metabolic syndrome associated with arterial hypertension, being one of the earliest symptoms in metabolic syndrome. An associated reduction in glomerular filtration rate is a sign of renal malfunction.

Arterial vessels dilation – a marker of aortic stiffness – is a prognostic factor for cardiovascular pathology and associated mortality.

It is agreed that metabolic syndrome is associated with rapid progression of the aortic stiffness process, proportionate to age, independent of other cardiovascular risk factors; arterial stiffness was also identified in other vascular territories as an early, premature vascular aging process.

Interestingly, comparisons on definitions of metabolic syndrome have been made by numerous prestigious establishments: the WHO set out for the first time the metabolic syndrome entity, including five current risk factors – diabetes mellitus/impaired glucose tolerance or insulin resistance plus 2 or more of the following factors: obesity (BMI > 30kg/m), triglycerides ≥ 150 mg%, HDL cholesterol < 35 mg% in men and < 39 mg% in women and blood pressure ≥ 140/90 mmHg. Scientific societies have similar reference values.

Some critics' views find that the definition criteria for metabolic syndrome are arbitrary, with no evidence-based fundamentals. One of the highlighted issues regarding the risk factors is that they should be rather continuous than assigned as present or absent. Cardiovascular risk increases with hyperglycemia, hypertension, and high LDL cholesterol levels.

Associated anomalies to metabolic syndrome point to increased gluconeogenesis, decreased glucose uptake in skeletal muscle, impaired vasodilation, increased platelet aggregation and oxidative stress and last, but not least, endothelial dysfunction as background [8,9].

A large proportion of glucose-intolerant, dyslipidemic, and insulin-resistant patients further develop hypertension and have already – as previously

mentioned – advanced endothelial dysfunction, which disrupts vascular dynamics and blood flow.

Being criticized for formerly specified reasons, metabolic syndrome represents more of a conceptual range of a complex pathology, with interconnected processes in a great measure, an enframed long-term relevant risk category. The Framingham risk score is considered to be superior as a short-term indicator; evaluation criteria, in this case, include age, gender, total cholesterol levels, LDL cholesterol, systolic blood pressure, coronary artery disease family history, smoking status and based on these, a risk prediction for a following coronary event in the next 10 years is provided [10].

In extended clinical trials, the impact of metabolic syndrome upon the prognostic of hypertension is consistent, and a couple of aspects should be underlined: the association between dyslipidemia and hypertension doubles the risk for cardiovascular and cerebrovascular events, but also cardiovascular mortality rate.

Analysis of the pathophysiological mechanism of metabolic syndrome has recently been suggested [11], comprising 3 elements: insulin resistance with fatty acids flow and excessive lipolysis. This process usually precedes type 2 diabetes mellitus occurrence. Insulin resistance decreases glucose transport and glycogen synthesis within the skeletal muscles, promoting lipid accumulation at the tissue level.

Free fatty acids inhibit glucose uptake in skeletal muscles and stimulate hepatic glycogenolysis, triglycerides and very-low-density lipoproteins production, with indisputable atherogenic effects [12].

The National Cholesterol Education Program slightly simplified the requirements for defining metabolic syndrome, demanding 3 out of the 5 following factors: abnormal waist circumference (≥ 102 cm in men and ≥ 88 in women), high triglyceride levels, low HDL cholesterol (< 40 mg% in men, < 50 mg% in women), high blood pressure (≥ 130 mmHg/ ≥ 85 mmHg) and elevated plasmatic fasting glucose (≥ 100 mg%).

In essence, it is acknowledged that most of the patients with metabolic syndrome, obesity, and a sedentary lifestyle have insulin resistance and compensatory hyperinsulinemia.

Metabolic syndrome is characterized by a proinflammatory and prothrombotic state, accompanied by glucotoxicity and lipotoxicity with metabolic and vascular anomalies [10].

The proinflammatory and prothrombotic status is determined by the adipose tissue, which is mainly in charge of the pathogenesis.

Adipose tissue has recently been considered an active endocrine and paracrine biological organ.

Consecutively to nutrient excess, adipocytes' hypertrophy and hyperplasia occur, causing excessive blood flow consumption and generating hypoxia. A cascade process is triggered; hypoxia leads to necrosis, macrophages infiltration, followed by adipocytokines and IL-1 and αTNF-like mediators production.

It is widely known that obesity induces oxidative stress, generating large amounts of reactive oxygen species at high NADPH oxidase expression and low antioxidant enzyme levels.

Through their mechanism of action, adipocytokines take part in the development of complex endocrine, paracrine, autocrine, or juxtacrine processes, controlling physiological or pathophysiological movements, such as food ingestion, insulin sensitivity, vascular sclerosis, immunity and inflammatory actions [13].

In metabolic syndrome, adipocytokines promote a low-leveled basal chronic proinflammatory state associated with other dysfunctions, namely dyslipidemia, insulin resistance, impaired coagulation, autoimmune diseases and most importantly, cardiovascular injuries. As a short reminder, foremost, atherosclerosis is an inflammatory process that aggravates endothelial dysfunction, systemically involving the vasodilation/vasoconstriction and atheromatosis/atherosclerosis balance.

The scientific debate pertaining to the first step, the initial mechanism in endothelial dysfunction, has not yet come to an end. Of course, it is utterly interesting to identify direct, efficient endothelial aggression. Is this initial dysfunction caused by a non-specific aggressive agent or by a more specific one?

It is common ground that insulin resistance triggers diabetes, which arises years before the onset of metabolic syndrome, being frequently (not mandatorily) associated with obesity and hypertension [14].

Adipocytes making up adipose subcutaneous and visceral tissue suffer hypertrophy with consequent cellular death and macrophage infiltration. In this context, cellular death was named pyroptosis [15] (pyroptosis represents one of the cellular death models – apoptosis, pyroptosis, paraptosis and necrosis; pyroptosis is a highly inflammatory form of programmed cell death) [16].

Crown-like structured macrophages that encircle dead adipocytes generate a more intense cytokine expression – a mechanism considered to be the beginning of insulin resistance and a strong link with regard to vascular pathology [14,17].

An atherogenic lipid panel is further established, characterized by an increased ratio of low-density to high-density lipids, associated with rising leptin levels and oxidative stress activation in endothelial vascular cells.

To sum up, all these proinflammatory and metabolic characteristics subsequent to obesity generate endothelial dysfunction – an early stage in atherosclerosis, hypertension, and diabetes [9].

A progressive functional alteration in vascular homeostasis emerges between vasoconstrictors (An-

giotensin II, Endothelin), vasodilators (NO, prostacyclins), atherogenic versus anti-atherogenic factors, procoagulants-anticoagulants, low-inflammatory endothelial-associated mechanism and vascular smooth muscle proliferation, hypertrophy, remodeling and apoptosis [18,19].

Reference shall be made on the C reactive protein (CRP). It serves as a proinflammatory and inflammation flag adipocytokine, involved in endothelial function and atherogenesis control to which we will later come back.

Oxidative reactions are essential triggers in atherogenesis, correlated with low-density lipoproteins oxidation. Early stages of atheroma plaque formation practically imply a multifactorial approach: inflammation, oxidative stress, endothelial dysfunction, platelets-endothelium interaction.

Metabolic syndrome - associated hypertension is frequently encountered, as it has previously been presented within the first pages of this paper, representing one of the five defining components of the syndrome at issue.

Arterial hypertension-associated disorders are often mentioned for characterizing metabolic syndrome, for instance, left ventricular hypertrophy, arterial stiffness, proteinuria.

The positioning statement of the European Society of Hypertension6 mentions several links involved in hypertension occurrence, with a comment regarding their dependence on obesity and insulin resistance. The referred factors concern: sympathoadrenal hyperactivity, renin-angiotensin-aldosterone system activation, impaired renal sodium excretion, and endothelial dysfunction [7].

Therapeutic approaches against metabolic syndrome aim, at their core, towards some major aspects: obesity – one fairly discouraging target [7]– insulin resistance and diabetes, atherosclerosis, and hypertension.

As the title of the paper implies, we will focus on pharmacology applied to arterial hypertension management. Pharmacological treatment of hypertension within the metabolic syndrome must take into account some significant landmarks: long-term therapy, which must imply few side effects, no negative drug interactions, and no interference with other organs' functionality incriminated in metabolic syndrome (glycemia, insulin sensitivity, atheromatosis, and others).

It is to bear in mind that separate analysis of some certain components of the metabolic syndrome has low or absent effects on target organs. However, after a comprehensive analysis, the picture is different. For instance, arterial hypertension determines left ventricular hypertrophy, aortic stiffness and microalbuminuria.

This clear tendency of hypertensive patients diagnosed with metabolic syndrome to develop a subclinical organ injury response, which anticipates cardiovascular events, explains the increase in morbidity and mortality rates in relation to the pertaining syndrome [20].

Putting aside some authorized opinions which state that metabolic syndrome is "not actually a syndrome" (a pathophysiological entity) and that each risk factor should be treated individually, we support the opposite side for which this constellation of risk factors and symptoms (actual, not prospective) is more efficient and adequate for the syndrome concept.

The fact that hypertension in diabetic patients is twice more frequent than in non-diabetics has great relevance regarding the evaluation and therapeutic attitude.

Furthermore, diabetes mellitus is 2-3 times more frequently found in hypertensive patients, suggesting an interesting etiologic interrelationship [21,22]. Microvascular impairment determined by diabetes mellitus includes nephropathy, neuropathy and retinopathy. Diabetes and hypertension are both risk factors for atherosclerosis. Thus, the incidence of coronary and cerebrovascular diseases is certainly immense [21].

Treatment must be initiated at blood pressure levels higher than 140/90 mmHg, with a therapeutic goal lower than 130/80 mmHg.

We will draw attention to drug treatment, with a brief mention of non-drug treatment, which is prospectively thought to improve blood pressure and glucose tolerance by increasing insulin sensitivity.

Diuretics and beta-adrenergic blocking agents are well known for reducing insulin sensitivity and increasing triglycerides levels.

Diabetes management is disturbed by beta-blockers, probably as a result of a beta-adrenergic mechanism of glycogenolysis inhibition. However, vasodilatory beta-blockers decrease peripheral vascular resistance and have limited effects on carbohydrate metabolism.

Another antihypertensive drug class that is prescribed in diabetes-associated hypertension is calcium channel blockers with no side effects on lipid metabolism, improving insulin sensitivity.

A recent analysis highlights the beta-blockers input for hypertension treatment, including comorbidities correlations [23].

Classical beta-blockers can have variable effects on the onset of diabetes, depending on the age, dose and treatment duration.

Resulting data from a meta-analysis shows that classical beta-blockers (such as Atenolol, Propranolol) increase the incidence of diabetes onset, in comparison with placebo [24].

On the other hand, compared with diuretics, classical beta-blockers (Atenolol, Propranolol, Metoprolol) determine a 26% fall in diabetes onset.

In contrast to calcium channel blockers, ACE inhibitors and A1 angiotensin II receptor blockers, previously mentioned beta-blockers, whether administered separately or associated with diuretics, increase the risk of a new diabetes onset by 21% and 23%, respectively [24].

There is a minor difference if we talk about vasodilatory beta-blockers such as Carvedilol and Nebivolol that can either benefit diabetes (specifically lipid and carbohydrates metabolism) or have no influence on diabetes. Carvedilol does not pose side effects on glycosylated hemoglobin, while Nebivolol significantly reduces it. From displayed data, Nebivolol does not induce fallouts on glycemic control [23].

Interestingly, analyzing ten years old available data from a prospective study (in which 12.550 non-diabetic patients aged between 45 and 64 were involved), it appears that hypertensive patients who received thiazide diuretics are not at a higher risk of developing diabetes as opposed to no treatment management. Noteworthy, hypertensive patients receiving beta-blockers (unspecified type) have a 28% greater risk for subsequent diabetes [25].

A meta-analysis (gathering 42 randomized clinical studies on over 190.000 patients) emphasizes that a lower diuretics dosage is superior to placebo in treating hypertension, the outcome aiming at the incidence of major cardiovascular events (coronary artery disease, heart failure, cerebrovascular accident, cardiovascular mortality, overall mortality). Under the mentioned endpoint background, no first-line antihypertensive drug class (ACE inhibitors, A1 angiotensin II receptor blockers, calcium channel blockers, alpha-blockers) has a more considerable efficiency than low-dose diuretics [26].

One group made of Mayo Clinic authors cite in their 2006 article the ALLHAT study, which concludes that thiazide diuretics comparably reduce all mortality sources and continue to play an important part in diabetes-associated arterial hypertensive treatment in synergy with ACE inhibitors and A1 angiotensin II receptor blockers altogether.

While investigating the well-known facts, the cited authors point out that thiazide diuretics worsen glycemic control depending on the dose while reducing insulin secretion and peripheral tissue insulin sensitivity.

Hypokalemia is adjusted with potassium supplements, simultaneously antagonizing the glucose intolerance effect induced by diuretics.

It has been recognized that diuretics, ACE inhibitors, and A1 angiotensin II receptor blockers association do have beneficial effects; angiotensin II receptor blockers antagonize side-effects of potassium on aldosterone secretion.

Beta-blockers are acknowledged insulin secretion inhibitors that concurrently reduce peripheral glucose oxidation (noticeable through weight gain), β2 adrenergic glycogenolysis stimulation in the pharmacodynamics context of relatively specific β1 blocking.

The new vasodilatory beta-blockers generation (third generation), among which we mention Carvedilol and Nebivolol, have a different medication safety standard, stimulating NO and antioxidants release, with potential insulin-regulating capacity and can be worst-case considered metabolically neutral (versus carbohydrates metabolism).

Vasodilatory beta-blockers, as opposed to classical beta-blockers, are implicitly preferred and become an actual option in diabetes-associated hypertension treatment.

Calcium channel blockers have beneficial effects as association therapy in hypertension linked to diabetes, outlined as lowering insulin resistance pharmacodynamic agents, without raising the incidence of diabetes onset for patients with metabolic syndrome.

To sum up, calcium channel blockers, whether dihydropyridines or non-dihydropyridines, increase tissue insulin sensitivity and improves pancreatic insulin secretion, with no compensatory sympathoadrenal impact consequent to insulin-sensitive tissue vasodilation.

Central acting antihypertensive agents are defined by α2 adrenergic receptors activation from the vasomotor center or by having selective effects on imidazoline II receptors, with a further decrease in peripheral sympathoadrenal activity.

Generally, central acting antihypertensive drugs have a favorable medication safety standard, with a relatively low incidence of side effects. Central sedative effects, sexual dysfunction and dry mouth, are especially mentioned, mediated by α2 central receptors activation, typical for Clonidine-associated drug class (including Guanfacine and α-methyldopa).

Moxonidine and Rilmenidine act as I1-receptor agonists located in the rostral, ventrolateral pressor and ventromedial depressor areas of the medulla oblongata.

Central-mediated low blood pressure is achieved with reduced peripheral sympathoadrenal tonus, with no consequences on heart rate or cardiac output. Through the formerly mentioned mechanisms, Moxonidine enhances insulin sensitivity and tissue glucose uptake.

Alpha-1 adrenergic peripheral receptor blockers have antihypertensive effects by competitively blocking alpha-1 adrenergic receptors located on particular effectors such as vascular smooth muscle cells. Their mechanism of action leads to a couple of side effects: tachycardia, dizziness, headache, general weakness. Nevertheless, they have substantially positive metabolic effects, increasing insulin sensitivity and high-density lipoproteins while reducing low-density lipoprotein levels.

This drug class (Prazosin, Terazosin, Doxazosin) is not among first-line treatments in hypertension-related to metabolic syndrome.

Pharmacologic control of the renin-angiotensin-aldosterone system in metabolic syndrome

Considering that diabetes (hyperglycemia) is the relevant clinical biomarker in metabolic syndrome, antihypertensive therapy must be aggressively enough, comprising proven beneficial therapy effects: ACE inhibitors, Angiotensin II receptor blockers, diuretics, calcium channel blockers (dihydropyridines) [27].

Drugs interfering with the renin-angiotensin-aldosterone system (ACE inhibitors and A1 angiotensin II receptor blockers) are the first-line option.

For patients having developed albuminuria, the initial treatment starts with ACE inhibitors or A1 angiotensin II receptor blockers.

The International Society of Hypertension Guidelines (2020) state that antihypertensive treatment must have a therapeutic target lower than 130/80 mmHg, recommending ACE inhibitors and association between diuretics and calcium channel blockers prior to anything [28].

Beta-blockers must be avoided in metabolic syndrome-related hypertension for the fact that they present an unacceptable risk of inducing type 2 diabetes [29].

High-dose thiazide diuretics can also increase diabetes onset risk. Associated beta-blockers and thiazides create a substantial diabetes risk.

At the same time, renin-angiotensin-aldosterone system inhibitors do not exacerbate glucose intolerance and can actually improve blood glucose levels. The cited authors recommend initial treatment with ACE inhibitors and A1 angiotensin II receptor blockers. Associations with this drug class have not been defined yet.

Medication that can worsen diabetes control are glucocorticoids; their hepatic metabolization stimulates glucose release and pulls back glucose from entering skeletal muscle cells (the major glucose uptakers).

Thiazide diuretics are the first option treatment in hypertensive patients. However, they are reputed for inducing high glycemic levels, as ALLHAT clinical study results show, increasing the risk of diabetes onset by 14% compared to calcium channel blockers or renin-angiotensin-aldosterone system blockers.

As previously mentioned, beta-blockers are involved in disrupting the pharmacologic control of diabetes.

A certified dangerous aspect is that during hypoglycemia, beta-blockers antagonize tachycardia, thus covering up symptomatology. Moreover, beta-blockers inhibit glycogenolysis, hepatic glucose release, as well as insulin release, even in the presence of hyperglycemia.

Association between beta-blockers and thiazides highly enhance diabetogenic risk.

Due to the synergistic negative effects of diabetes and dyslipidemia characterizing metabolic syndrome, related arterial hypertension deserves a more aggressive treatment, meaning that therapeutic targets should be lower than the usual ones, below 130/80 mmHg. This target was established in consensus with the "SPRINT" trial, which was concluded before the due date, after approximately 3 years instead of 5, for ethical reasons [30].

A lower risk of either fatal or non-fatal cardiovascular events or all-cause mortality was correlated with a systolic pressure therapeutic target, using an intensive treatment, below 120 mmHg, in opposition with a 140 mmHg target. The intensive-treatment group experienced significantly more side effects and was even more difficult to monitor [31].

Brief commentaries and conclusions

Diuretics have broadly been a relevant antihypertensive therapy, usually prescribed as a first option treatment. Their altogether antihypertensive effects – water, sodium and other electrolytes renal excretion – reduce the plasma volume; additionally, sodium excretion diminishes vascular sympathoadrenal reactivity, generating vasodilation. Diuresis – the main effect of this drug class, although relatively poor, does not owe its exclusive cause of the antihypertensive effect.

Our experimental data (not published yet) show that thiazide diuretics (i.e., hydrochlorothiazide) induce vascular relaxation and uncompetitively antagonize noradrenaline effects on isolated rabbit aorta, shifting the dose-response curve to the right (using graphical processing of this correspondence). The emergence of other agents in the antihypertensive pharmacotherapeutic arsenal, such as renin-angiotensin-aldosterone system inhibitors or calcium channel blockers, has somehow faded away diuretics' importance.

It is worth mentioning the use of Indapamide, Chlorthalidone, or chronic thiazide-like diuretics in antihypertensive therapy. Fast-acting and intense diuretics, for instance, Furosemide, are used in the emergency treatment of hypertension.

Thiazides and thiazide-like diuretics are identified under the general "thiazides" term, although their mechanisms of action, safety standards and efficacy profiles are different. The main differences are in favor of thiazide-like diuretics: increased

antihypertensive efficacy, reduced electrolytic and metabolic side effects.

Diuretics are recommended especially for diabetes-related hypertension, old patients with ischemic stroke history, heart failure, isolated systolic hypertension and resistant hypertension [32].

First-line therapy in diabetes-associated hypertension is ACE inhibitors. Given the pathological context, these patients have a tendency to store water and are at high risk of heart failure or renal failure [33].

Meta-analyses emphasize the significantly low heart failure risk in diabetic patients with adequate treatment of both hypertension and diabetes.

Despite the well-known side effects, diuretics are preferably used aside renin-angiotensin-aldosterone inhibitors, but thiazide-like diuretics such as Chlorthalidone and Indapamide are preferred for their long-term effects (hydrochlorothiazide half-life: 8-12h; indapamide half-life: 12-24h; chlorthalidone half-life: 50-60h). The acting time of the three diuretics is approximately 24 hours. Generally, diuretics are most frequently associated with renin-angiotensin-aldosterone inhibitors, and there is a particular preference for thiazide-like diuretics.

There is an intriguing outcome deriving from clinical studies, especially from the ALLHAT study, which states that lowering blood pressure itself is more important to reduce the implicit risks than the utilized medication to achieve it.

Renin-angiotensin-aldosterone (RAA) system inhibitors (ACE inhibitors or A1 angiotensin II receptor blockers) must not be associated with one another. Simultaneously, depending on the clinical necessities, RAA inhibitors are combined with diuretics – for instance, with Chlorthalidone or Indapamide – or with calcium channel blockers. The maximum dose of RAA inhibitors will remain the first-line treatment in hypertensive diabetics with albumin to creatinine ratio >300 mg/g.

Beta-blockers are excluded from antihypertensive first-line therapy in diabetic patients [34].

Conflict of Interest

The author confirms that there are no conflicts of interest.

References

1. Voicu V, Dorobantu M. Hypertension and heart failure. In: Dorobantu M, Mancia G, Grassi G, Voicu V, eds. Switzerland: Springer Nature Switzerland AG; 2019:430.
2. Zwieten PA van, Viser FC. Metabolic Syndrome: pharmacologic treatment. Hear Metab. 2006;(30):15-2o.
3. Reaven GM. The insulin resistance in human disease. Diabetes. 1988;5:364-371. doi:10.2337/diab.37.12.1595.
4. Reaven GM. The metabolic syndrome: Requiescat in Pace. Clin Chem. 2005;51(6):931-938. doi:10.1373/clinchem.2005.048611.
5. Raeven GM. The metabolic syndrome: is this diagnosis necessary? Am J Clin Nutr. 2006;5(84):1253. doi:10.1093/ajcn/83.6.1237.
6. Redon J, Cifkova R, Laurent S, et al. The metabolic syndrome in hypertension: European society of hypertension position statement. J Hypertens. 2008;26(10):1891-1900. doi:10.1097/HJH.0b013e328302ca38.
7. van Zwieten P, Visser F, van Zwieten PP. Metabolic Syndrome: Pharmacological Treatment.
8. Tabit CE, Chung WB, Hamburg NM, Vita JA. Endothelial dysfunction in diabetes mellitus: Molecular mechanisms and clinical implications. Rev Endocr Metab Disord. 2010;11(1):61-74. doi:10.1007/s11154-010-9134-4.
9. Su Y, Liu XM, Sun YM, Wang YY, Luan Y, Wu Y. Endothelial Dysfunction in Impaired Fasting Glycemia, Impaired Glucose Tolerance, and Type 2 Diabetes Mellitus. Am J Cardiol. 2008;102(4):497-498. doi:10.1016/j.amjcard.2008.03.087.
10. Johnson LW, Weinstock RS. The metabolic syndrome: Concepts and controversy. Mayo Clin Proc. 2006;81(12):1615-1620. doi:10.4065/81.12.1615.
11. McCracken E, Monaghan M, Sreenivasan S. Pathophysiology of the metabolic syndrome. Clin Dermatol. 2018;36(1):14-20. doi:10.1016/j.clindermatol.2017.09.004.
12. Metabolic Syndrome: Practice Essentials, Background, Pathophysiology.; 2017.
13. Lago F, Dieguez C, Gómez-Reino J, Gualillo O. Adipokines as emerging mediators of immune response and inflammation. Nat Clin Pract Rheumatol. 2007;3(12):716-724. doi:10.1038/ncprheum0674.
14. Petrie JR, Guzik TJ, Touyz RM. Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms. Can J Cardiol. 2018;34(5):575-584. doi:10.1016/j.cjca.2017.12.005.
15. Giordano A, Murano I, Mondini E, et al. Obese adipocytes show ultrastructural features of stressed cells and die of pyroptosis. J Lipid Res. 2013;54(9):2423-2436. doi:10.1194/jlr.M038638.
16. Guzik TJ, Touyz RM. Oxidative stress, inflammation, and vascular aging in hypertension. Hypertension. 2017;70(4):660-667. doi:10.1161/HYPERTENSIONAHA.117.07802.
17. Ferrannini E, Buzzigoli G, Bonadonna R, et al. Insulin Resistance in Essential Hypertension. N Engl J Med. 1987;317(6):350-357. doi:10.1056/NEJM198708063170605.

18. Creager MA, Lüscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease. Pathophysiology, clinical consequences, and medical therapy: Part I. Circulation. 2003;108(12):1527-1532. doi:10.1161/01.CIR.0000091257.27563.32.
19. Savoia C et al. Vascular inflammation and endothelial dysfunction in experimental hypertension. Int J Hypertens. 2011;2011. doi:10.4061/2011/281240.
20. Mulè G. Metabolic syndrome in hypertensive patients: An unholy alliance. World J Cardiol. 2014;6(9):890. doi:10.4330/wjc.v6.i9.890.
21. Chapter 7. Hypertension complicated by other diseases. Hypertens Res. 2014;37(4):315-324. doi:10.1038/hr.2014.10.
22. Shimamoto K, Ando K, Fujita T, Hasebe N, Higaki J. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014).; 2014. doi:10.1038/hr.2014.20.
23. Ram CVS. Beta-blockers in hypertension. Am J Cardiol. 2010;106(12):1819-1825. doi:10.1016/j.amjcard.2010.08.023.
24. Bangalore S, Messerli FH, Kostis JB, Pepine CJ. Cardiovascular Protection Using Beta-Blockers. A Critical Review of the Evidence. J Am Coll Cardiol. 2007;50(7):563-572. doi:10.1016/j.jacc.2007.04.060.
25. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and Antihypertensive Therapy as Risk Factors for Type 2 Diabetes Mellitus. N Engl J Med. 2000;342(13):905-912. doi:10.1056/NEJM200003303421301.
26. Psaty BM, Lumley T, Furberg CD, et al. Health Outcomes Associated with Various Antihypertensive Therapies Used as First-Line Agents: A Network Meta-analysis. J Am Med Assoc. 2003;289(19):2534-2544. doi:10.1001/jama.289.19.2534.
27. Lee AM, Gurka MJ, DeBoer MD. Correlation of metabolic syndrome severity with cardiovascular health markers in adolescents. Metabolism. 2017;69:87-95. doi:10.1016/j.metabol.2017.01.008.
28. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020;75(6):1334-1357. doi:10.1161/HYPERTENSIONAHA.120.15026.
29. Blaha MJ, Bansal S, Rouf R, Golden SH, Blumenthal RS, DeFilippis AP. A practical "ABCDE" approach to the metabolic syndrome. Mayo Clin Proc. 2008;83(8):932-943. doi:10.4065/83.8.932.
30. Wright JTJ, Williamson JD, Whelton PK, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015;373(22):2103-2116. doi:10.1056/NEJMoa1511939.
31. Burns NS, Miller PW. Learning What We Didn't Know — The SPRINT Data Analysis Challenge. N Engl J Med. 2017;376(23):2205-2207. doi:10.1056/NEJMp1705323.
32. Burnier M, Bakris G, Williams B. Redefining diuretics use in hypertension: Why select a thiazide-like diuretic? J Hypertens. 2019;37(8):1574-1586. doi:10.1097/HJH.0000000000002088.
33. Bahtiyar G, Gutterman D, Lebovitz H. Heart Failure: a Major Cardiovascular Complication of Diabetes Mellitus. Curr Diab Rep. 2016;16(11). doi:10.1007/s11892-016-0809-4.
34. Cutler JA, Davis BR. Thiazide-Type Diuretics and β-Adrenergic Blockers as First-Line Drug Treatments for Hypertension. Circulation. 2008;117(20):2691-2705. doi:10.1161/CIRCULATIONAHA.107.709931.

