



Hypertension and diabetes mellitus in women: a high-risk combination

Hipertensión y diabetes mellitus en la mujer: una combinación de alto riesgo

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INTRODUCTION

Mortality in women due to cardiovascular disease is a national and global problem. The relationship between type 2 diabetes mellitus (T2DM) and systemic arterial hypertension (SAH) is complex and bidirectional. In T2DM, different conditions lead to SAH, while some mechanisms in the latter contribute to a more significant alteration in insulin resistance and the development of T2DM. Both pathologies act synergistically at the micro and macrovascular levels, which can lead to higher mortality.

Risk factors related to gender have not been fully clarified. The coincident pathophysiological mechanisms of SAH and T2DM in women are also differentially affected by the stages of their lives and hormonal variations. Treatment recommendations are similar for women and men; however, the reproductive stage, risk assessment, and possible adverse effects must be considered in women.

In this review, mechanisms and factors that favor SAH in patients with T2DM are pointed out, aspects of the treatment of both conditions are also reviewed, and the differences in some therapeutic responses are related to gender.

Diabetes mellitus (DM) and systemic arterial hypertension (SAH) are two entities that coincide for a long time in their evolution. SAH is a significant risk factor for cardiovascular disease (CVD), chronic kidney disease (CKD), and stroke, frequently affecting DM patients. In turn, DM is more common among patients

with SAH. The latter occurs in 50 to 70% of patients with type 2 diabetes mellitus (T2DM) and 30% among patients with type 1 diabetes mellitus (T1DM).^{1,2} Evidence suggests that insulin resistance contributes to the pathogenesis of SAH, which is a factor that frequently precedes the development of T2DM.¹⁻³ Pathophysiological mechanisms and overlapping risk factors are fundamental in the coexistence of SAH and DM, increasing mortality risk and micro and macrovascular complications. Shared pathophysiological mechanisms contributing to the co-occurrence of both diseases include insulin resistance, endothelial dysfunction, inflammation, dysautonomia, and inappropriate activation of the renin-angiotensin-aldosterone system (RAAS) and atherosclerosis (*Figure 1*). These mechanisms can increase sodium absorption, sympathetic activity, vasoconstriction, inflammation, and oxidative stress.⁴ Other associated mechanisms include activation of epithelial sodium channels, alteration of extracellular vesicles and their microRNAs, alteration of the intestinal microbiota, and increased activity of the renal sodium-glucose cotransporter.

Angiotensin II can lead to insulin resistance at the skeletal muscle level by decreasing blood flow, inhibiting intracellular insulin-triggered signaling pathways, and impairing insulin secretion from pancreatic beta cells. Estrogens present variability in their concentration, producing different responses in the mentioned mechanisms. Estradiol is a determining hormone in controlling several mechanisms that affect

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insulin resistance and the vascular system, in addition to the RAAS. Estradiol deficiency leads to changes in immune function, dysregulation of the RAAS, and modification of the anti-inflammatory response.⁵

The differences between women and men in systolic blood pressure are more accentuated in patients with DM than in non-diabetics, and the difference is more apparent after 55.^{1,4} On the other hand, the SAH control rate is 33.6% in men and 30.6% in women, and it is lower in the population with diabetes compared to non-diabetic patients.¹ The factors and conditions that mark the differences between men and women in SAH and DM are diverse (Figure 2).

TREATMENT

The goals of treatment with changes in lifestyle and drugs must be individualized, considering cardiovascular risk, possible adverse drug reactions (ADR) to antihypertensives, and the patient's characteristics.⁶⁻⁸

In patients with T2DM and blood pressure (BP) levels greater than 130/80 mmHg, it is recommended to start antihypertensive drug treatment. The recommended goal is < 130/80 mmHg.^{7,8} In pregnant women with diabetes

and arterial hypertension, a blood pressure threshold of 140/90 mmHg for initiation and treatment adjustment is associated with better pregnancy and neonatal outcomes.⁸

Hygienic-dietary measures. Lifestyle modifications are the initial steps for treating hypertension in patients with diabetes and should always be recommended for patients with BP > 120/80 mmHg.^{7,8}

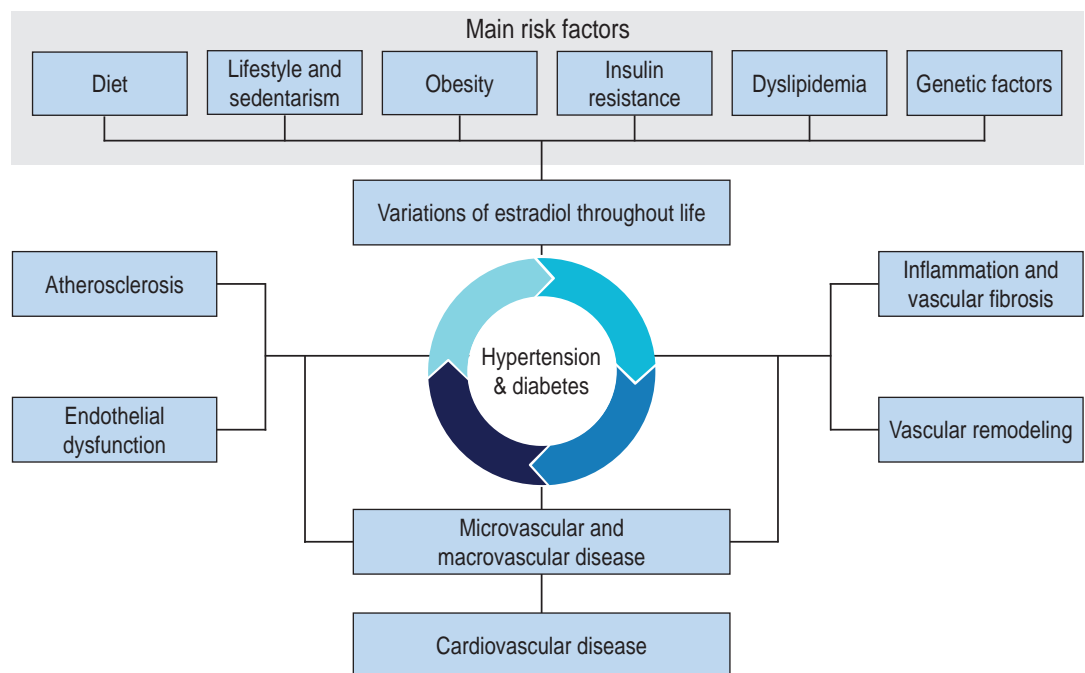
These generally include reducing body weight, a DASH-like eating pattern [consumption of fruits and vegetables (8-10 servings per day) and low-fat dairy products], moderate-aerobic physical activity (> 150 minutes/week), restriction in sodium intake (< 2,300 mg/day) and avoiding excessive alcohol consumption (no more than one serving per day in women).⁸

These measures improve the efficacy of some antihypertensives, favoring metabolic and vascular health and reducing ADR.^{7,8}

Pharmacotherapy. Drug treatment should be started or adjusted in patients with diabetes and BP ≥ 130/80 mmHg, establishing a regimen of two or more drugs in those with BP > 160/100 mmHg.^{7,8} The choice of antihypertensive is similar in men and women, but the reproductive stage and adverse effects must also be considered in women.³

Figure 1:

The pathophysiological mechanisms that arterial hypertension and diabetes mellitus share include insulin resistance, obesity, dyslipidemia, genetic factors, and lifestyle, and they are affected by estrogen concentration, which presents variations in the different stages of women.



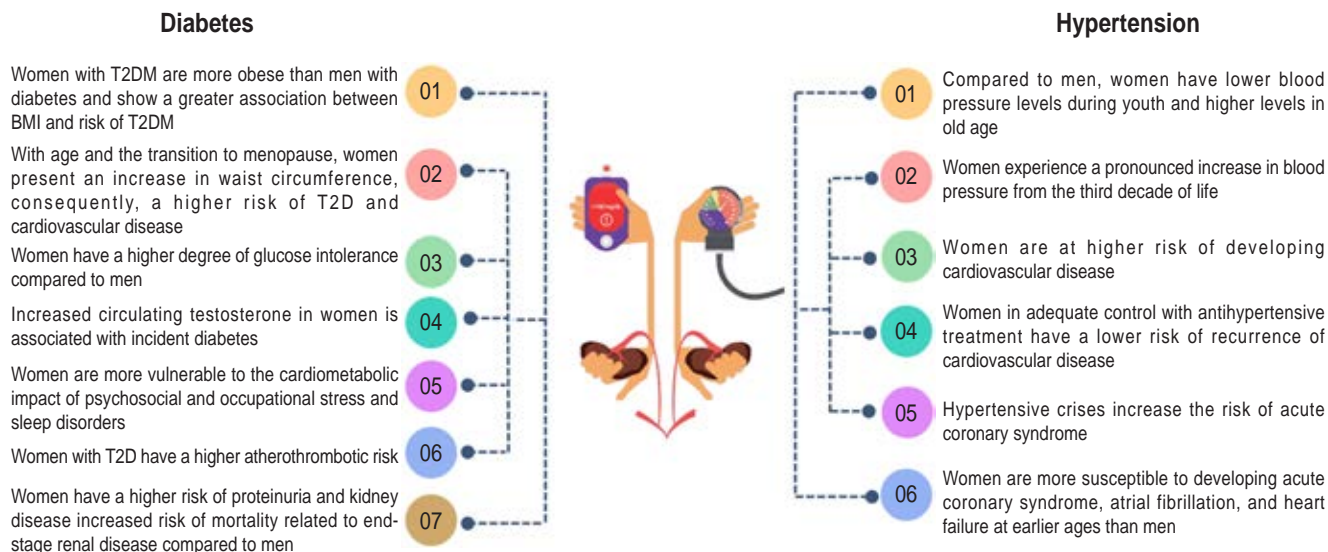


Figure 2: The pathogenesis and clinical presentation of arterial hypertension and diabetes mellitus present differences according to sex and gender.

Angiotensin-converting enzyme 2 inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARB) are the recommended first-line treatment in patients with DM.⁸ In patients with diabetes, arterial hypertension, and urinary albumin/creatinine ratio of > 30-299 mg/g, especially > 300 mg/g, ACE inhibitors or ARB are recommended at the maximum tolerated dose.⁸ In patients with diabetes and hypertension who do not achieve blood pressure goals using three classes of antihypertensives (including a diuretic), treatment with mineralocorticoid receptor antagonists such as spironolactone should be considered.^{7,8}

Hypoglycemic agents with cardiovascular benefit. Sodium-glucose cotransporter type 2 (SGLT2i) inhibitors and GLP-1 receptor agonists (aGLP-1) have been shown to have beneficial cardiovascular effects, partly attributed to BP reduction.⁷ SGLT2i are associated with a mild diuretic effect and a reduction in systolic/diastolic BP of 3-6/1-2 mmHg.^{9,10} In contrast, aGLP-1 produces a decrease in BP of 2-3/0-1 mmHg.¹¹

Complications. SAH in patients with DM conditions is a greater risk of cardiovascular events, heart failure, deterioration of microvascular complications (nephropathy and retinopathy), and mortality.^{7,8} According to the ACCORD study^{12,13} and J-DOIT3,¹⁴

an optimal BP control reduces these complications. Regarding gender, women have more adequate rates of hypertensive control; however, their therapeutic adherence is lower. The BP threshold associated with cardiovascular risk is lower in women than men; likewise, target organ damage^{15,16} and treatment-resistant hypertension is more common.¹⁷ To date, no significant differences in the efficacy of antihypertensives have been confirmed according to gender; however, a higher prevalence of ADR has been reported in women.^{15,16}

CONCLUSION

Relationship between type 2 diabetes mellitus (T2DM) and systemic arterial hypertension (SAH) in women is complex and involves many pathophysiological mechanisms that lead to endothelial dysfunction, micro and macro vascular disease, that increase their cardiovascular risk. Pharmacological treatment must be optimized to achieve therapeutic goals and reduce cardiovascular complications.

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